THE UNIVERSITY *of* EDINBURGH

Investigations into Aryne Chemistry

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of the degree of Doctor of Philosophy

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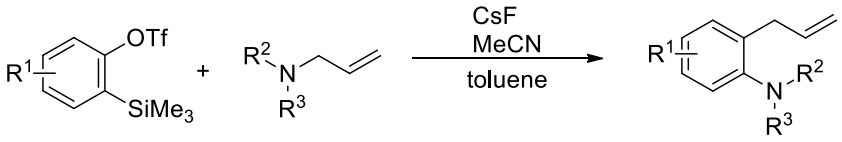
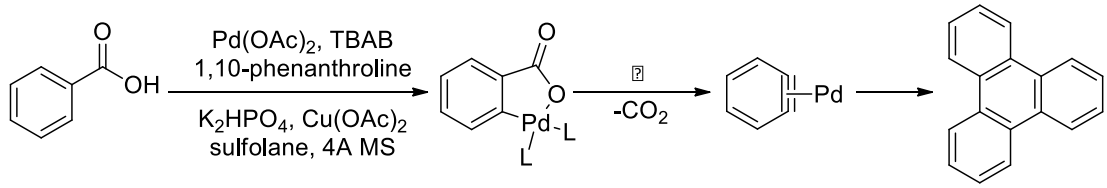
Abstract

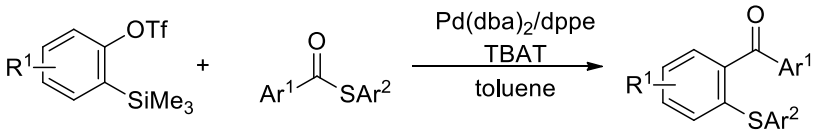
The first project in this thesis describes our research reacting arynes with tertiary allyl amines to generate functionalised anilines *via* a benzyne induced aza-Claisen reaction. This process works in good to excellent yields and the methodology can be further applied to make benzannulated medium sized ring amine systems.



The second project covered in this thesis details our studies in the generation of benzyne from benzoic acid. This process utilises palladium catalysis involving an *ortho* C-H activation of benzoic acid which generates a 5 membered palladacycle. This palladacycle then spontaneously decomposes with heat to generate palladium bound benzyne and carbon dioxide. The yield of benzyne was monitored by observing the amount of triphenylene formed in the process. Further synthetic applications in this process were limited, but it was shown that the benzyne could be reacted with alkynes to generate phenanthrene and naphthalene products.



The third project in this thesis details our work on the insertion of benzyne into the C–S bond of thioesters. Using palladium catalysis and an *o*-trimethylsilylphenyl triflate benzyne precursor, a variety of thioethers were produced. The yields for this reaction were moderate to good but it was found that only aromatic substituents were tolerated on the thioester.



Contents

Acknowledgements

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A big thank you also goes to Mark, Fiona, Adele, Lynne, Lorna and the rest of the Sutherland group for teaching me the difference between a hyphen and a dash and making me feel welcome in a new home.

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Finally I would like to thank my family for their love and support throughout my PhD. My mum and dad for encouraging me to always aim higher, my wife, Claire for her unending patience through 9 years of studentship and my daughter Sophie for making us laugh every day.

Author's Declaration

This thesis represents the original work of Alastair Alexander Cant unless explicit reference is made to the contribution of others in the text. The research was carried out in the Joseph Black Building at the University of Edinburgh under the supervision of Dr Michael F. Greaney.

Portions of the work described herein have been published elsewhere as listed below:

A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem. Int. Ed*. **2009**, 48, 5199-5202.

A. A. Cant, L. Roberts, M. F. Greaney, *Chem. Commun.*, **2010**, 8671-8673.

Abbreviations

°C	degrees celcius
µL	microlitre
µmol	micromoles
Ac	acetyl
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
Boc	tert-butoxycarbonyl
bpt	boiling point
Bu	butyl
cod	cyclooctadiene
Cy	cyclohexyl
dba	dibenzylideneacetone
DCM	dichloromethane
DMAc	dimethylacetylene
DMAD	dimethylacetylenedicarboxylate
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dpph	1,2-bis(diphenylphosphino)hexane
dppm	1,1-bis(diphenylphosphino)methane
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
EWG	electron withdrawing group
g	grams
GCMS	gas chromatography mass spectrometry

h	hours
HMDS	hexamethyldisilazane
iPr	isopropyl
JACS	Journal of the American Chemical Society
L	ligand/litre
LDA	lithium diisopropylamine
M	Molar
Me	methyl
MeCN	acetonitrile
mL	millilitre
mmol	millimoles
mol	moles
mpt	melting point
MS	molecular seives
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
No.	number
O/N	overnight
Ph	phenyl
ppm	parts per million
PTC	phase transfer catalyst
rac	racemic
RB	round bottomed
RT	room temperature
SIMes	2,4,6-trimethylphenyl
TBAB	tetra-*n*-butylammonium bromide
TBAC	tetra-*n*-butylammonium chloride
TBAI	tetra-*n*-butylammonium iodide
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
tBu	tertiary butyl

TCC	three component coupling
Temp	temperature
Tf	triflouromethane sulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	toluene
triflate	trifluoromethane sulfonate

1 Introduction

1.1 Methods of Generating Arynes

The organic chemist now has access to a vast selection of methods for the generation of arynes, all of which have both pros and cons to their use. This introduction will detail some of the more popular methods for the generation of arynes as well as reviewing some of the more contemporary methods recently developed.

The first recorded evidence of arynes was published by the German scientists Stoermer and Khalert in 1902.[1] They found that when 3-bromobenzofuran was treated with strong base in ethanol they yielded 2-ethoxybenzofuran as product. This product was unexpected as the expected S_NAr mechanism should yield only the 3-ethoxy-derivative. This anomaly was recorded, but was not fully explained and it was only later that aryne intermediacy was proposed as a mechanism to explain the unusual regiochemistry of these reactions.[2]

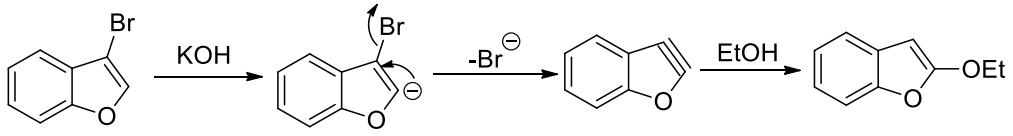


Fig. 1.1.1. The reaction of 3-bromobenzofuran with potassium hydroxide and ethanol.

This method of aryne generation is well developed and involves the use of strong bases to *ortho*-deprotonate halo aromatics such as **2** which then decompose to give benzyne (figure 1.1.2.). It is a firmly established route to *o*-benzyne and there are numerous examples in the literature of its use.[3-7]

Over the years numerous new methods were developed to generate arynes in addition to the method discovered by Stoermer and Khalert. Some of the more popular classical methods for generating arynes are detailed in figure 1.1.2.

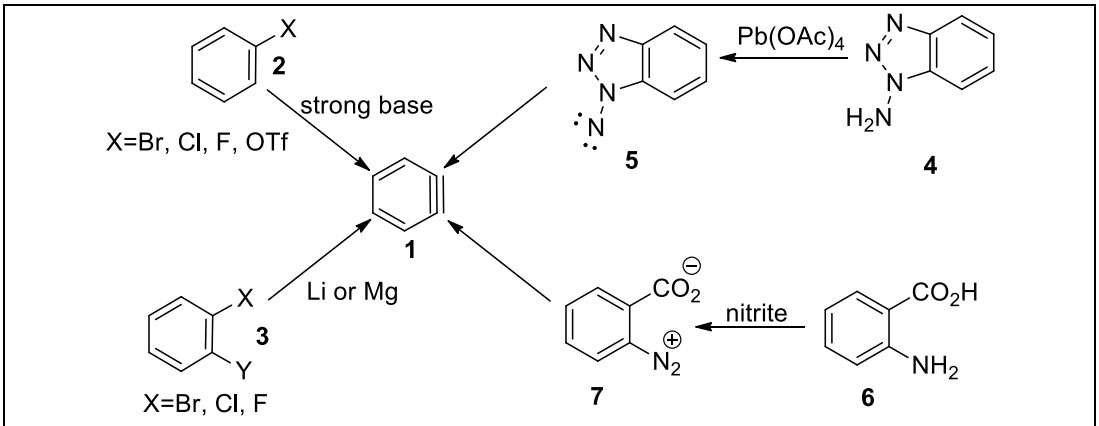


Fig. 1.1.2. Classical methods for the generation of arynes.

The use of 1,2-disubstituted halo aromatics such as **3** as benzyne precursors is also well documented.[8-11] This method was developed by Wittig *et al* in the 1950's as part of his work into the investigation of the "aryne mechanism".[11] The method involves a halogen exchange when 1,2-disubstituted haloaromatics are treated with stoichiometric amounts of either magnesium or lithium. The resulting metallated species then undergo a 1,2-elimination to generate benzyne. This strategy has a significant advantage over the mono-halogenated method as total regiocontrol of benzyne formation is possible.

Two of the more recent classical approaches involve the generation of benzyne from aminobenzotriazole **4** and anthranilic acid **6**. The generation of benzyne from aminobenzotriazole was first published by Rees and co-workers in 1969. The method involves a mild oxidation of the triazole to the nitrene **5** which then fragments into two molecules of nitrogen and benzyne.[12]

The generation of benzyne from anthranilic acids was published in 1963 by Friedman *et al*. The treatment of cheap and readily available anthranilic acid with nitrite leads to the formation of the zwitterionic intermediate **7**. This intermediate decomposes on heating to generate nitrogen, carbon dioxide and benzyne.[13] If effort is made to isolate the zwitterionic intermediate **7**, this is an efficient and clean method for the generation of benzyne and is still used today.[14, 15] It must be noted however, that this is indeed a hazardous way to generate benzyne. The zwitterionic intermediate **7**, if

isolated, is extremely explosive and great care must be taken when handling these experiments.[16]

All of the methods described in figure 1.1.2. are well known and are taught in most undergraduate courses and textbooks.[9] They all, however, have major drawbacks which have restricted the development of aryne chemistry. The requirement of strong bases, oxidants, stoichiometric amounts of metals or explosive intermediates limited the compatibility of aryne chemistry with current literature.

This was all to change in 1983 when the Kobayashi group developed a novel method for the generation of arynes which proceeded under mild conditions. When the *o*-triflatosilane benzyne precursor **8** is treated with a caesium fluoride, at room temperature, in acetonitrile, a 1,2 elimination is induced which yields benzyne in near quantitative yields (figure 1.1.3.).[17] The fact that this chemistry could be performed at room temperature, without recourse for harsh reagents and in high yields, allowed a renaissance of aryne chemistry.

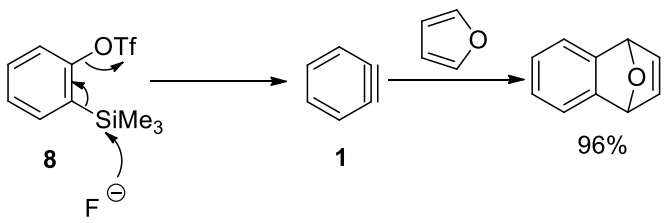


Fig. 1.1.3. The generation of benzyne from *ortho*-trimethylsilylphenyl triflate **8**.

The classical reactions, such as electrocyclisation reactions[18-23] and nucleophilic addition to benzyne[24-26] were revisited with the new and improved benzyne precursor. It was soon found that these reactions were easy to perform, giving clean transformations, increased substrate scope and high yields.

In addition to this, entirely new areas in aryne chemistry were soon developed. The insertion of arynes into sigma bonds using *o*-triflatosilanes has been extensively reviewed and has been found to be a useful synthetic tool for the formation of *ortho*-substituted aromatic rings.[27, 28] In addition to this, the use of benzyne in

transition metal catalysed reactions was also found to work. The seminal work by Yamamoto and co-workers[29-31] and Pena *et al*[32-35] into the palladation of benzyne, laid the foundation stones for a vibrant research area which is still active today.

1.2 The Organometallic Capture and Generation of Arynes

During the early 1990's it was found that aryne chemistry could be combined with transition metal catalysed chemistry to provide an incredibly efficient synthetic tool for the difunctionalisation of aromatic rings. The earliest reports on the palladation of benzyne focussed on its trimerisation either with itself, to generate triphenylenes **9**, or with alkynes to generate phenanthrenes **10** and naphthalenes **11**.[29, 32, 34]

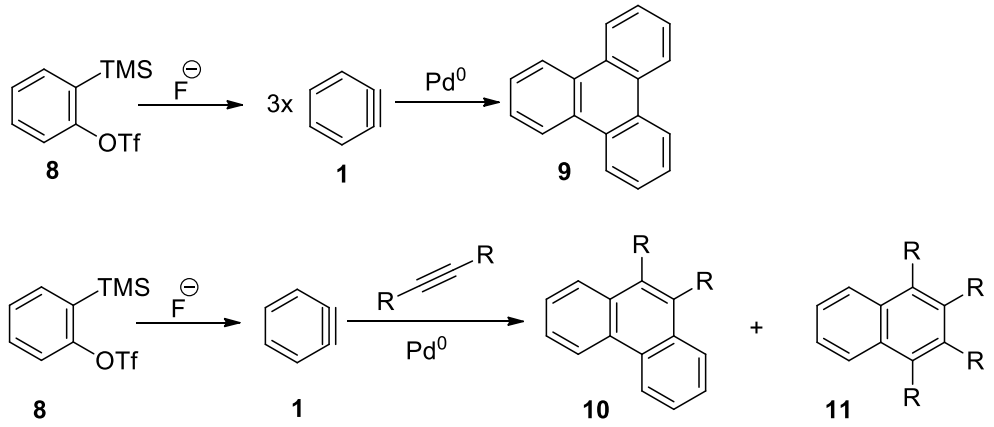


Fig. 1.2.1. The palladium catalysed trimerisation of arynes.

The discovery of aryne palladation lead to an increased interest in the research area. The application of this chemistry soon diversified and it was discovered that this chemistry could be used in a variety of different scenarios. The insertion of benzyne into standard palladium catalysed reactions such as Heck reactions[36] and Stille couplings[37, 38] was found to be an effective strategy in the synthesis of disubstituted arenes.

An example of benzyne insertion into a Heck reaction is detailed in figure 1.2.2 below. The reaction begins in a similar manner to the Heck reaction with an oxidative addition of Pd(0) into the C–X bond to generate the palladated species **12**. Benzyne generated from **8** then inserts into the C–Pd bond of **12** to give the biphenyl species

13. The Heck reaction then occurs between this species and the olefin **14** to eventually give the disubstituted aromatic product **16**.

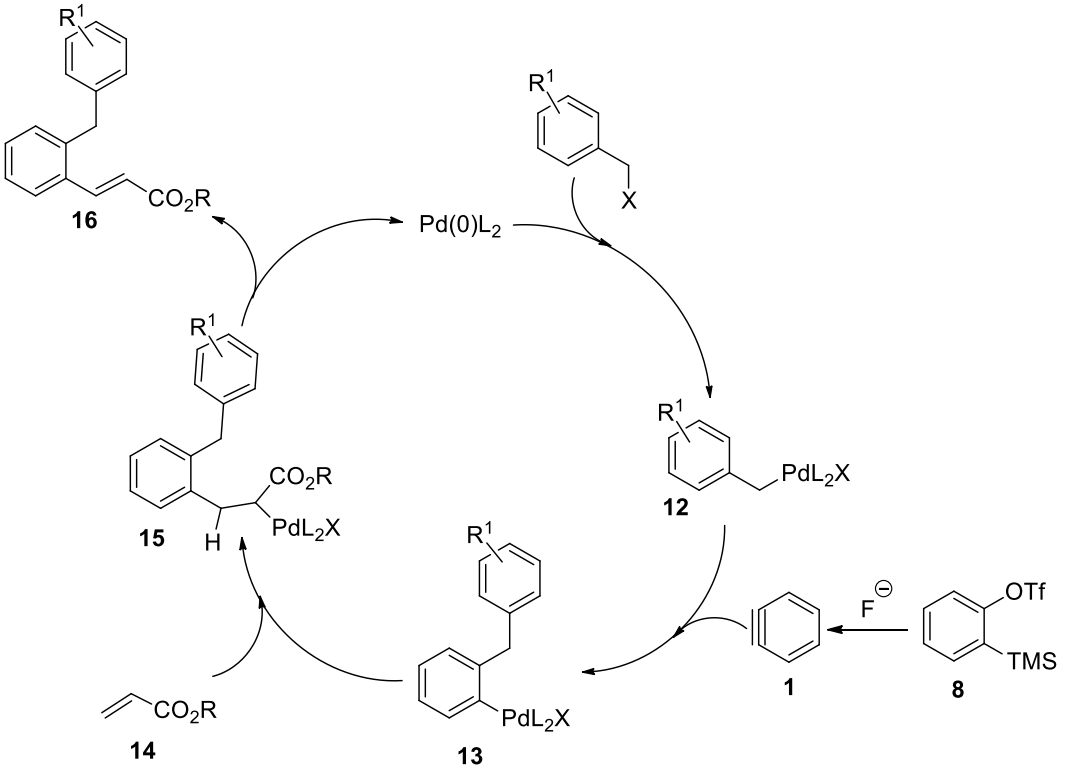


Fig. 1.2.2. The three component Heck coupling of benzyne.[36]

There is vast scope for the use of transition metal catalysed aryne chemistry and an excellent review covers the literature up until August 2006.[8] This literature review will cover all subsequent literature on the organometallic generation and capture of arynes.

1.3 Organometallic Methods for Generating Arynes

Encouraged by the success of Kobayashi's *o*-trimethylsilyltriflate benzyne precursor **8**, many groups have tried to mirror his success through researching different methods of generating benzyne. Importantly, these groups wanted to maintain the benzyne compatibility with organometallic chemistry. Over the past 4 years there have been 3 new methods for generating benzyne using palladium catalysed transformations.

The first of these was published by Hu and co-workers in 2006.[39] The Hu group developed a novel strategy to generate palladium bound arynes from 1-chloro-2-haloaromatics. By treating these compounds with palladium(II) acetate in an oxidative addition/ transmetallation pathway, the palladium bound benzyne species **17** could be produced. This species was then cross coupled with the Grignard reagent **19** to give the transmetallated species **18** which upon C–H activation would generate fluorene **20**. The reactions proceeded well giving yields between 68 and 92% using a variety of different dihaloaromatics. In addition to this, the reaction was also shown to work well with 1-tosyl-2-haloaromatics.

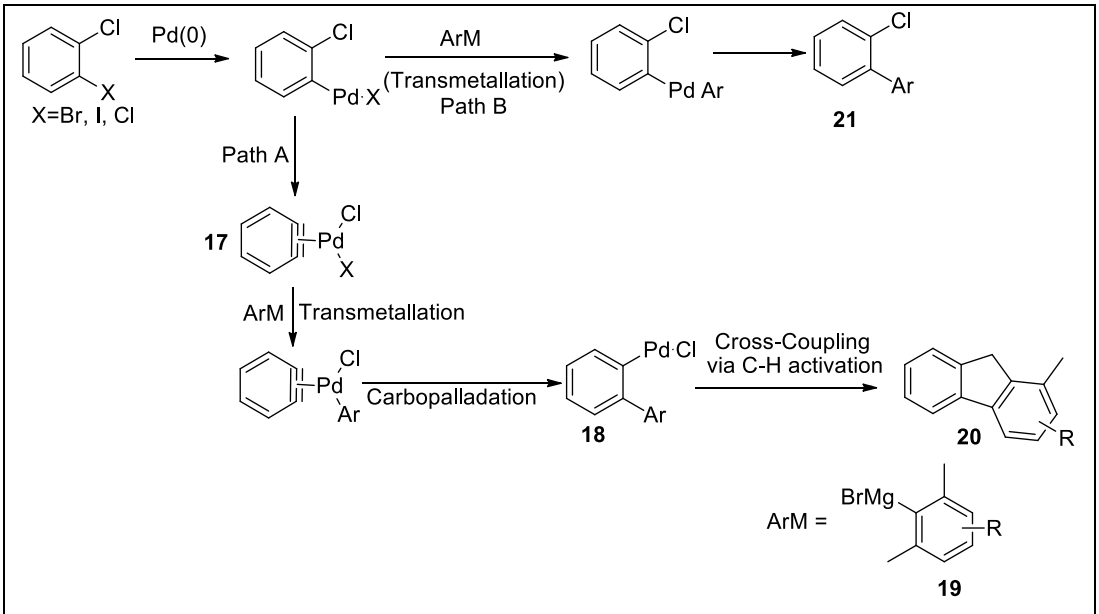


Fig. 1.3.1. The generation of arynes from 1-chloro-2-haloaromatics.[39]

The main competing pathway for this reaction involved a non-benzyne mechanism which is illustrated as path B. Selectivity for path A over B could be obtained by

ensuring that no phosphine or N-heterocyclic carbene ligand were used in the reaction. Optimised conditions yielded only trace amounts of the by-product **21**.

Later publications by the Hu group built on the success of this paper and expanded the substrate scope for aryne generation to include a variety of different 1,2-dihaloarenes and 2-haloaryl arenesulfonates.[40, 41]

The second paper published recently on aryne generation was published in 2008 by Kim *et al*.[42] Whilst investigating palladium catalysed C–H activation procedures, the observation of unusual decarboxylative by-products led the group to develop a new method for aryne generation.

The method generates palladium bound benzyne from the reaction of *ortho*-substituted benzoic acid esters or benzoic acids with a catalytic amount of palladium(II). The reaction begins with an oxidative addition of the haloarene with palladium(II) to generate the intermediate **23**. It is then hypothesised that this intermediate undergoes a δ-Carbon elimination and concomitant elimination of carbon dioxide. The palladium bound benzyne then undergoes the well known [2+2+2] trimerisation to generate the triphenylene **24** which was used to quantify yields.

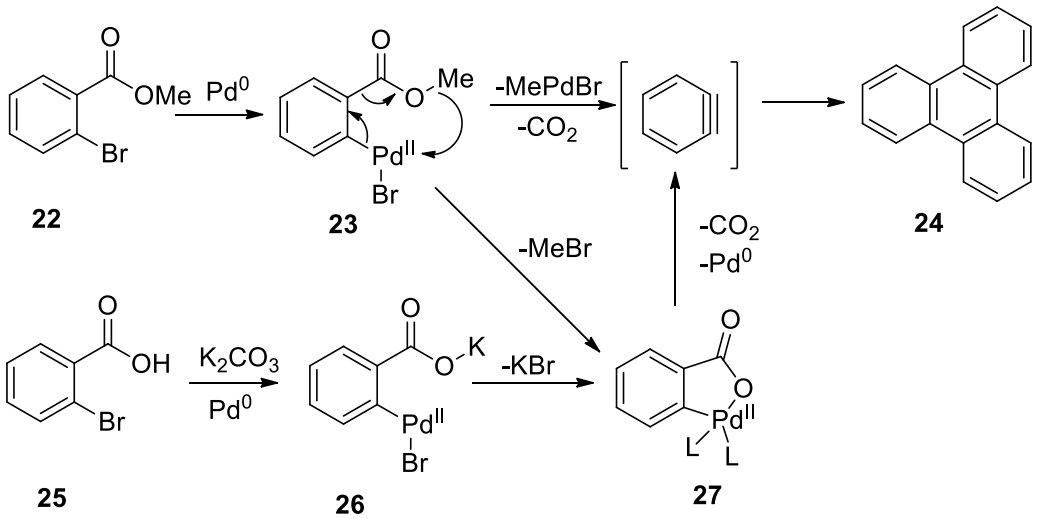


Fig. 1.3.2. The generation of benzyne from *ortho*-halo benzoic acids and esters.[42]

Overall, the yields of triphenylene for the process were found to be moderate at best, with very little substrate scope explored and thus this methodology is limited in its applications.

Although the yields for aryne formation for the process developed by Kim were low, the concept behind the process is an interesting one. The theory that arynes can be generated from the decomposition of palladacycle **27** provided the suitable inspiration for the third new method of generating benzyne – the generation of benzyne from benzoic acids.[43] This method was developed recently in the Greaney group and an in-depth discussion can be found in chapter 3 of this thesis.

1.4 Transition Metal Catalysed Aryne Reactions.

The main body of research into transition metal catalysed aryne reactions utilise palladium sources as the catalyst. The research into these reactions can be broadly categorised into three main areas – three component couplings, cyclisations and trimerisations of arynes.

1.4.1 Palladium Catalysed Three Component Couplings of Benzyne

Three component couplings (TCCs) of benzyne are a powerful class of synthetic methodologies which allow the construction of complex products through the combination of several simple starting materials. Broadly speaking, the methodology is based around the concept that benzyne can insert itself into palladium catalysed reaction mechanisms generating disubstituted arenes as products.

Following on from the success of the three component couplings of alkyl halides, *tert*-butyl acrylate and benzyne,[36] Greaney and co-workers further developed their methodology on TCCs to include aryl halides. In a similar fashion to the work described previously in figure 1.2.1, the methodology was further expanded to include aryl iodides as starting materials. The synthesis of biaryl compounds of the type **28** was achieved in 38–91% yields with 18 examples showing good substrate scope in addition to the synthesis of a small biologically active example.[44]

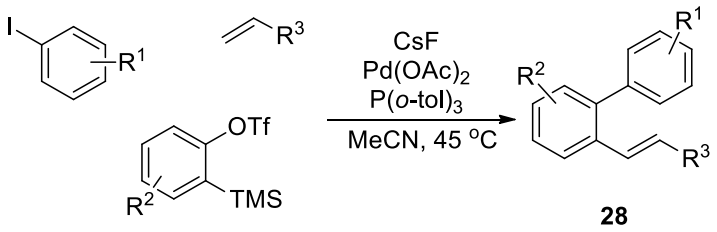


Fig. 1.4.1.1. The three component Heck coupling of arynes.

Another group which has had a significant impact on the TCC of arynes is the Cheng group. As the above publication shows, this methodology can be applied to typical

palladium catalysed transformations such as Heck couplings. Cheng and co-workers further expanded the methodology when they applied the chemistry to Suzuki, Stille and Hiyama couplings.[45]

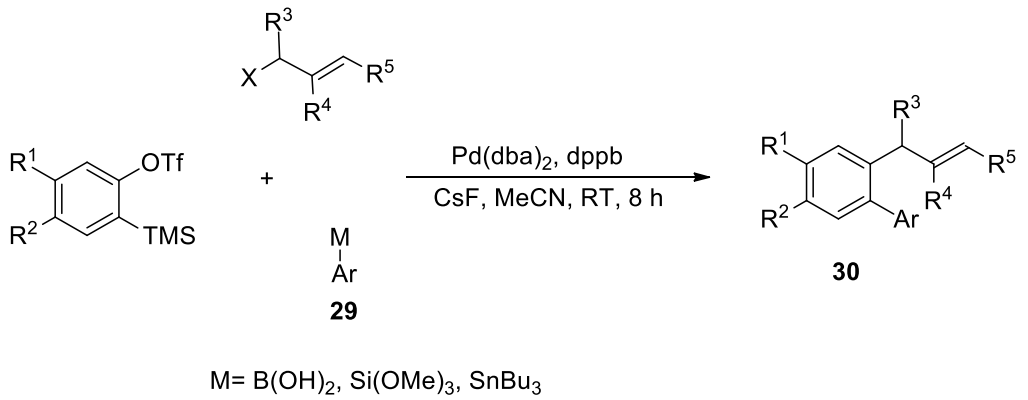


Fig. 1.4.1.2. The three component Stille, Suzuki and Hiyama couplings of arynes.[45]

Having achieved success in developing these TCCs with classical transition metal catalysed reactions, Cheng then built on his success in the field by incorporating a relatively new synthetic methodology into his three component coupling.[46]

The use of bicyclic alkenes for the *ortho* C–H activation of aryl iodides has received significant attention in recent years.[47-50] The methodology utilises compounds such as norbornadiene **31** to activate aryl iodides for coupling reactions. Cheng and co-workers employ this methodology in combination with aryne chemistry to provide an elegant one-pot procedure to yield 1,10-dihydrophenanthrene derivatives in good to excellent yields (figure 1.4.1.3).

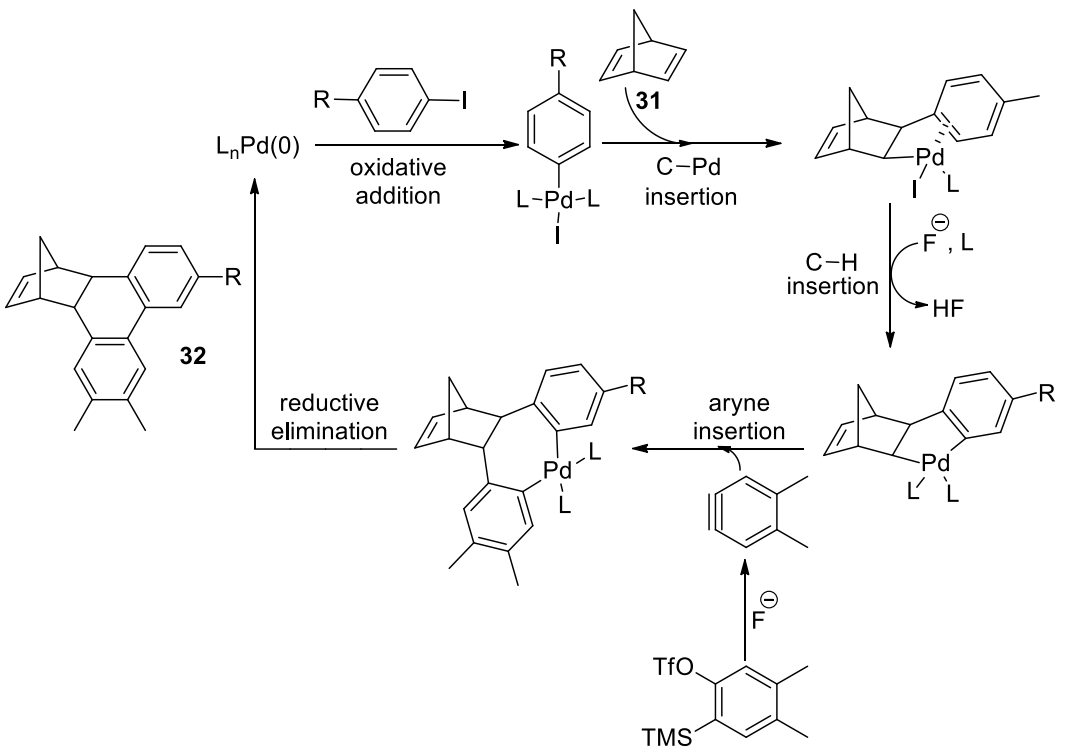


Fig. 1.4.1.3 The three component coupling of an aryl iodide, bicyclic alkene and benzyne.[46]

More recently the Cheng group have focussed their attention on incorporating Sonogashira type couplings into their TCCs. These couplings utilise a transmetallation step of an alkynyl copper species with an aryl palladium species. This is illustrated in figure 1.4.1.4. The figure illustrates the coupling of allylic acetates or halides with terminal alkynes and benzyne. The reaction is promoted *via* the formation of the alkynal cuprate species **33**, which arises from the reaction of copper(I) iodide and the terminal alkyne **34**.[51]

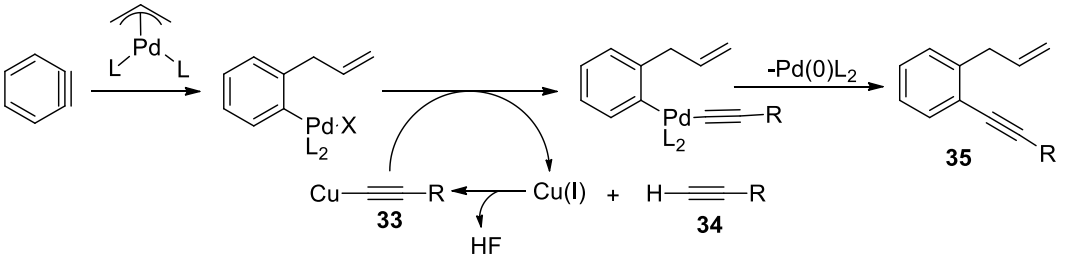


Fig. 1.4.1.4. The coupling of allylic acetates or halides with terminal alkynes and benzyne.[51]

The second of the two papers published by Cheng in this field is similar to that described above. The process as described in figure 1.4.1.5. is similar as it uses both palladium and copper catalysis to react terminal alkynes, arynes and an electrophile. Differences arise however, when the mechanism is investigated. Interestingly, the benzyne is not carbopalladated in the first instance, but instead reacts with the alyknyl cuprate species **36** first. It is the organocuprate **37** that then undergoes the transmetallation to give the disubstituted aromatic compound **38** as product. In this example, the allylic palladium species **39** is generated from the allylic epoxide **40**; this is the first instance of its use as an electrophile in these reactions.[52]

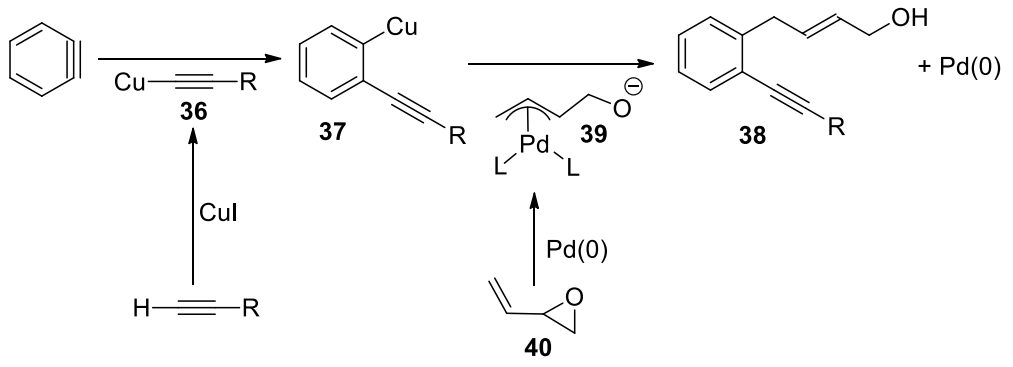


Fig. 1.4.1.5. A cooperative copper and palladium-catalysed TCC of benzynes, allylic epoxides, and terminal alkynes.[52]

The use of allylic palladium species in these TCCs is very popular and an interesting example of its use in combination with carbonylation chemistry was published recently by Li and co-workers.[53] The reaction uses allylic acetates to form the allylic palladium species and the TCC proceeds in a similar way as described before. The reaction finishes however, with a cyclocarbonylation step instead of a straightforward coupling. The reaction produces dihydro-1*H*-inden-1-ones of the types **41a** and **41b**, where the regiochemistry of the reaction can be dictated through the use of the appropriate ligand.

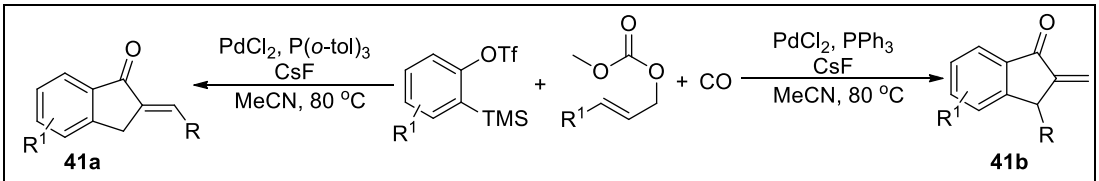


Fig. 1.4.1.6. Palladium-catalysed cyclocarbonylation of arynes with methyl allyl carbonates.[53]

The last example of a TCC also employs a cyclisation step as part of its mechanism. The reaction combines alkynes, arynes and aryl halides in a sequential three component cross coupling (figure 1.4.1.7). The reaction yields phenanthrenes either as a single regioisomer or a mixture of two possible regioisomers in good to excellent yields. The role of TlOAc in the reaction is unclear at present but it is thought that it may have a role in removing the halide from the solution.[54]

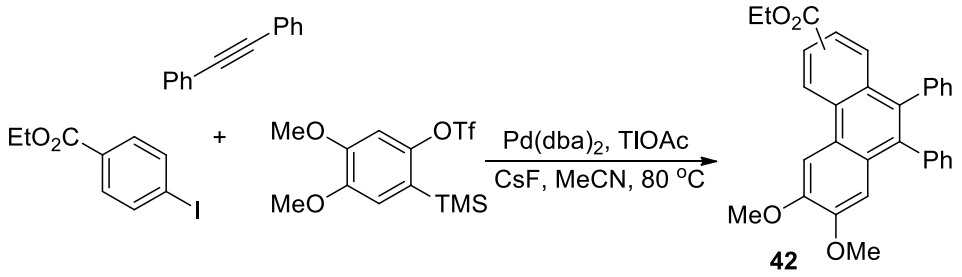


Fig. 1.4.1.7. The palladium-catalysed sequential, three component cross-coupling of aryl halides, alkynes and arynes.[54]

1.4.2 Intramolecular Three Component Couplings

Buoyed by their success in the field of three component couplings, the Larock group decided to investigate the possible uses of this technology in intramolecular processes. By appending the so called 'third component' *ortho* to an aryl halide, it was decided that should the reaction proceed as predicted, then intramolecular cyclisation methodologies could be developed. The Larock group first applied this theory to the reaction of 2-haloarenecarboxaldehydes **43** with arynes (figure 1.4.2.1.) and found that the reaction was very successful generating fluoren-9-ones in good yields.[55]

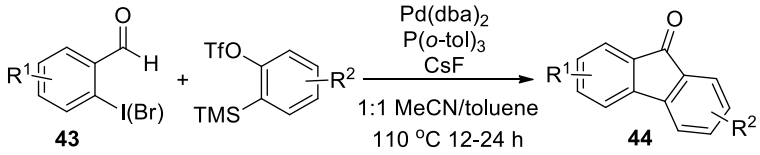


Fig. 1.4.2.1. Synthesis of fluoren-9-ones by the palladium-catalysed annulation of arynes by 2-haloarenecarboxaldehydes.[55]

This strategy was further developed in the Larock laboratory when the scope of the reaction was further expanded to include *o*-halostyrenes and *o*-haloallylic benzenes. The *o*-halostyrenes reacted in a manner similar to that of the 2-haloarenecarboxaldehydes and gave 9-fluorenylidenes **47** in good yields. The *o*-haloallylic benzenes furnished 9,10-phenanthrenes albeit in moderate to poor yields.[56, 57]

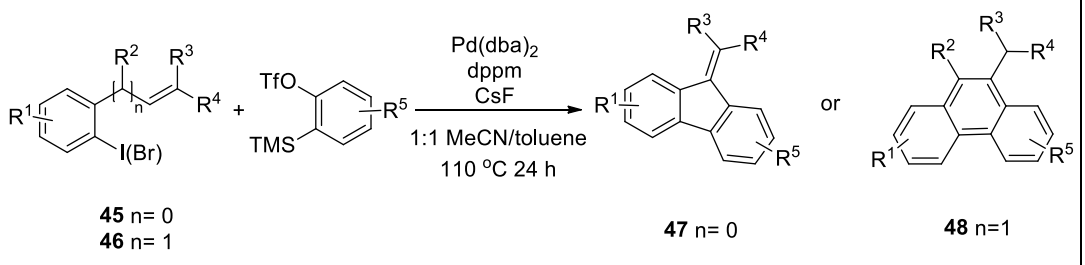


Fig. 1.4.2.2. Synthesis of 9-fluorenylidenes and 9,10-phenanthrenes through palladium-catalysed aryne annulation by *o*-halostyrenes and *o*-haloallylic benzenes.[56, 57]

Two possible mechanistic pathways are proposed for these reactions as illustrated in figure 1.4.2.3. Both pathways proceed *via* the palladium bound intermediate **52**, which, through the mechanism illustrated, yields the products **53** and **54**. In path a, the aryne generated from **8** coordinates with Pd(0) directly, affording palladium bound benzyne **49**. This complex then undergoes oxidative addition with the aryl halide **50** to generate the arylpalladium(IV) complex **51**. Reductive elimination of **51** then affords palladium complex **52**. In path b, oxidative addition of **50** to give **55** is the first step and this is then followed by a benzyne insertion into the carbon-palladium bond to give **52**.

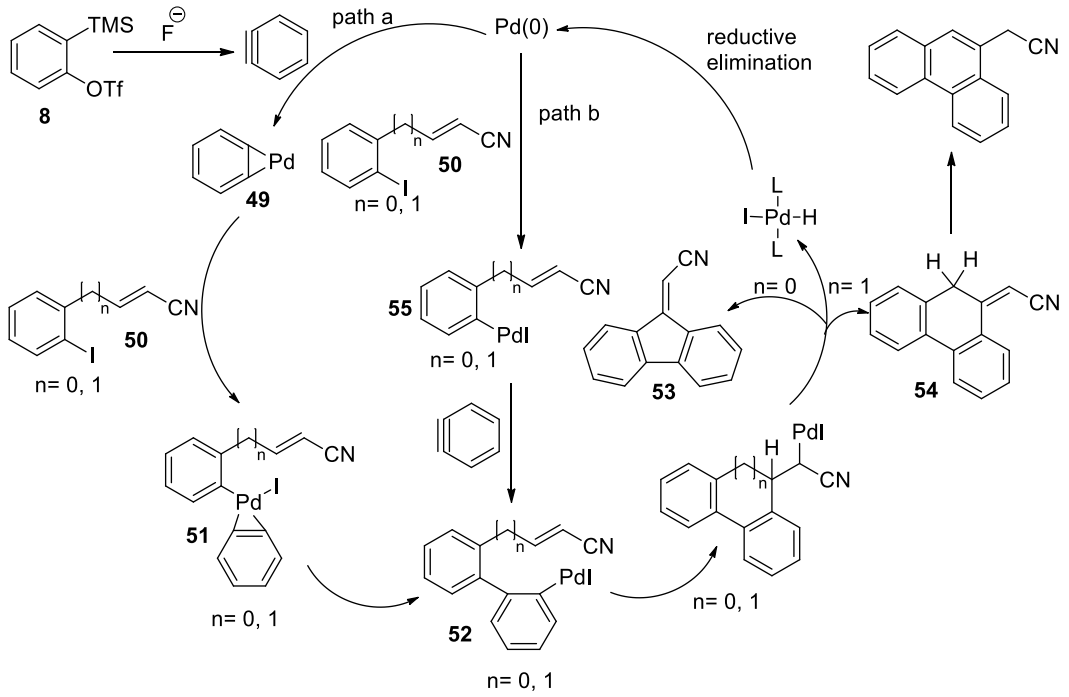
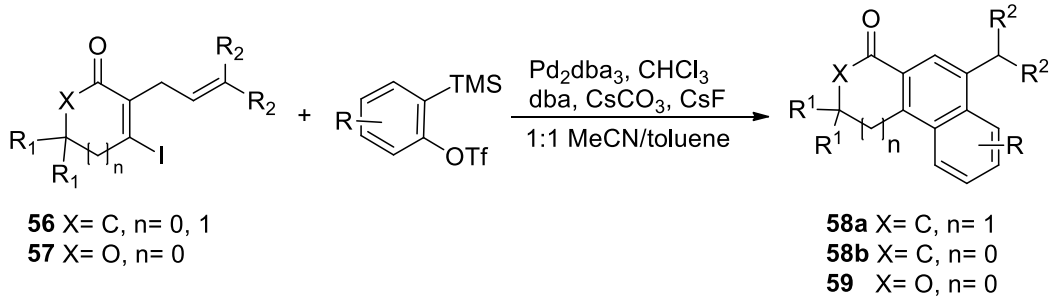


Fig. 1.4.2.3. Possible mechanisms for the formation of 9-fluorenylidenes and 9,10-phenanthrenes from benzyne and *o*-halostyrenes and *o*-haloallylic benzenes.[56, 57]

The reaction scope was further expanded this year when Huang *et al* and Li *et al* published some interesting works in this field. Huang expanded the scope of these reactions further by applying the methodology to substituted vinyl iodides. Using conditions similar to those developed by Larock *et al*, Huang reacts 2-allyl-3-iodocyclohexanones and pentanones **56** with benzyne to generate hydrophenanthren-1(2H)-ones **58a** and naphtho [2,1-c]furan-3(1H)-ones **58b** respectively in good yields. The reaction scope is then further expanded when the furanone derivatives **57** are

employed. These substrates generate interesting naphtho [2,1-c]furan-3(1*H*)-ones **59** which are structurally important in both pharmaceuticals and as building blocks in organic synthesis.[58]

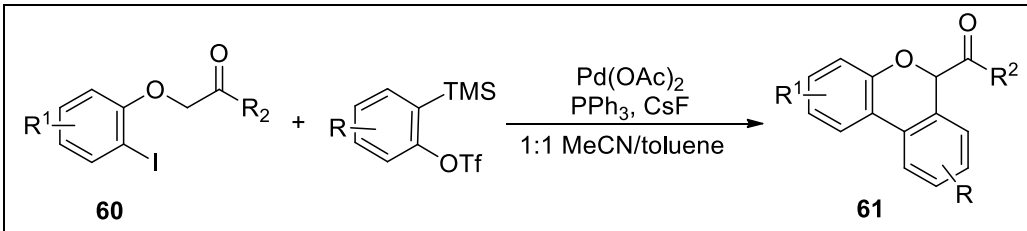


56 X= C, n= 0, 1
57 X= O, n= 0

58a X= C, n= 1
58b X= C, n= 0
59 X= O, n= 0

Fig. 1.4.2.4. Synthesis of hydrophenanthren-1(2*H*)-ones and naptho[2, 1-c]furan-3(1*H*)-ones**.**[58]

The work performed by Li *et al* is slightly different in that the functional group *ortho* to the halide has to be activated *via* base mediated deprotonation. The 2-(2-iodophenoxy)-1-substituted ethanone starting materials **60**, when reacted with arynes, yield benzochromenes **61** as products in medium to good yields.[59]



60 **61**

Fig. 1.4.2.5. Palladium catalysed annulations of arynes with 2-(2-iodophenoxy)-1-substituted ethanones.[59]

1.4.3 Aryne Annulations Coupled With C–H Activation

As this review has shown, there is tremendous scope for the application of aryne annulation in organic synthesis. The above TCCs show the reactions of palladium bound arynes, with two separate activated functional groups, to achieve the formation of two new carbon-carbon bonds attached to a benzene ring. It is interesting to note however, that aryne annulations can actually be coupled with C–H activation technologies. The palladium-catalysed carbocylisation of aryl iodides with benzyne is an emerging research area which clearly illustrates the synthetic applicability of aryne annulations.

The first examples of this methodology were published by Larock and co-workers[60] in 2005 and detail the synthesis of fused polycyclic aromatics by palladium catalysed annulation of arynes using halobiaryls. This reaction again works on the principle of the insertion of an aryne into a palladium-carbon bond. The novelty in this chemistry however, arises from the insertion of palladium into the C–H bond of the starting material which enables the formation of the triphenylene products **62**.

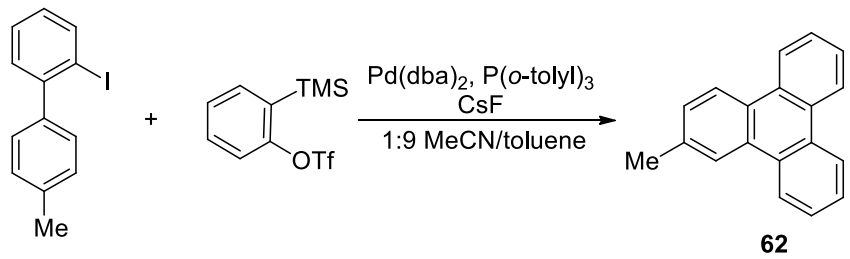


Fig. 1.4.3.1. The synthesis of fused polycyclic aromatics by palladium catalysed annulation of arynes using halobiaryls.[60]

In similar work, Cheng and co-workers can generate similar triphenylenes using simple haloaromatics. The reaction works *via* an oxidative addition and benzyne insertion of the haloaromatic species **63**, which then undergoes C–H insertion to give the 5-membered palladacycle **64**. Benzyne insertion then follows to furnish the triphenylene species **65**.[61]

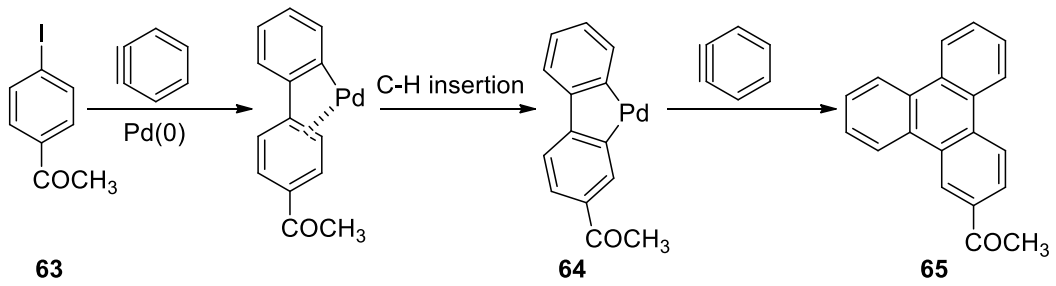


Fig. 1.4.3.2. Palladium catalysed carbopalladation and carbocyclisation of arynes with aryl halides.[61]

Both of these processes are powerful synthetic methodologies for the formation of fused polycyclic aromatics and the full scope and mechanism of both reactions were recently explored by the Larock group.[62] The synthetic applicability of this chemistry has recently been demonstrated in the synthesis of novel rylenebis(dibaroximide) dyes, where triphenylene subunits were constructed through aryne annulation.[63]

Additional work in this area was published by Zhang and co-workers. Indolo-phenanthridines **67** are widely found in natural products and show a broad spectrum of biological activities. This group decided to utilise aryne annulations in order to produce these substrates from the reaction of arynes with 1-(2-bromophenyl)-1*H*-indoles **66**.[64]

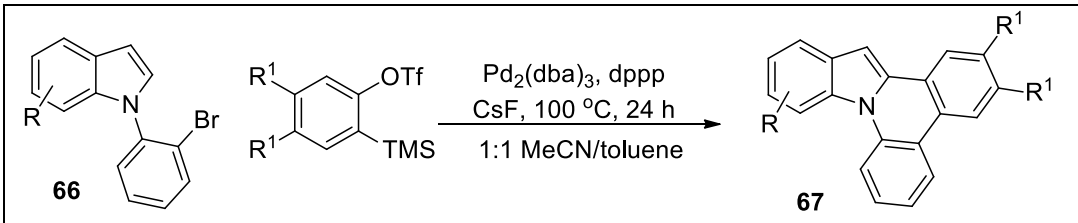


Fig. 1.4.3.3. Synthesis of indolo[1,2-*f*]phenanthridines from palladium-catalysed reactions of arynes.[64]

An interesting approach to the synthesis of phenanthridines and isoquinolines using aryne chemistry also falls into this class of reaction. Zhu and co-workers found that the palladium catalysed reaction of acyloximes with arynes could be used to make these products in medium to good yields through a C–H activation mechanism.[65]

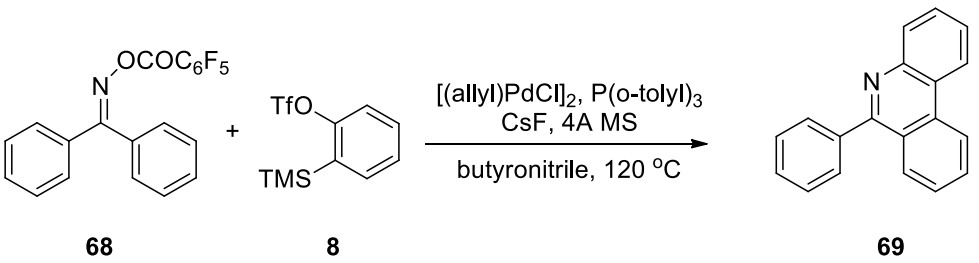


Fig. 1.4.3.4. The synthesis of phenanthridines **69** from acyl oximes **68** and benzyne.[65]

1.4.4 Palladium Catalysed [2+2+2] Cycloadditions

The early work on palladium catalysed [2+2+2] cycloadditions focussed almost entirely on either the self trimerisation of benzyne or the co-trimerisation of benzyne with alkynes (figure 1.2.1).[29, 32, 34, 35] This methodology set the foundations for palladium catalysed aryne chemistry and has found recent use in natural product synthesis. Sato *et al* used the intramolecular cotrimerisation of alkynes with benzyne to synthesise the advanced intermediate **70**. This intermediate was then used to make the natural arylnaphthalene lignans Taiwanins C & E. In addition to this, the related compound dehydrodesoxypodophyllotoxin, was also made using this methodology.[66]

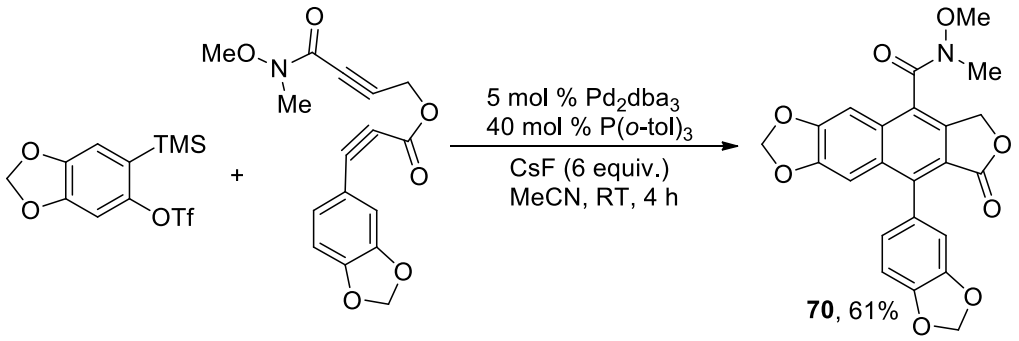


Fig. 1.4.4.1. The synthesis of intermediate **70** through a [2+2+2] cycloaddition of benzyne.[66]

An enantioselective variation of this methodology has also been developed by Guitain and co-workers. Helicenes such as **71** have been synthesised previously using the [2+2+2] cycloadditions of arynes, but never enantioselectively. The potential use of these compounds as chiral ligand precursors led the group to research an enantioselective variation of the synthesis. The best results were obtained using a

chiral BINAP ligand, in THF with caesium fluoride as a fluoride source. Enantiomeric excesses of up to 67% could be achieved albeit in the poor yield of only 16%.[67]

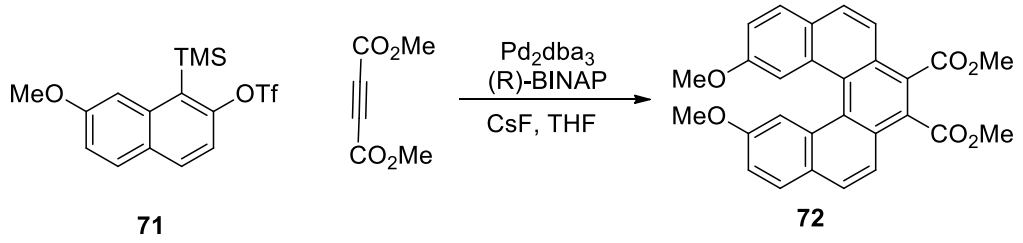


Fig. 1.4.4.2. The synthesis of helicene **72** using a palladium catalysed [2+2+2] trimerisation of arynes.[67]

In recent years however, scientists have been looking to expand the scope of this reaction beyond alkynes and investigations into other unsaturated systems have been explored.

The logical extension of this methodology was to apply the chemistry to olefinic systems. This work was performed by the Guitain group and was used to synthesise dihydrophenanthrene derivatives. The methodology only worked with electron withdrawing groups attached to the olefin and it was found that the reaction could be steered to the formation of biaryls **74** if the ligand was changed.[68]

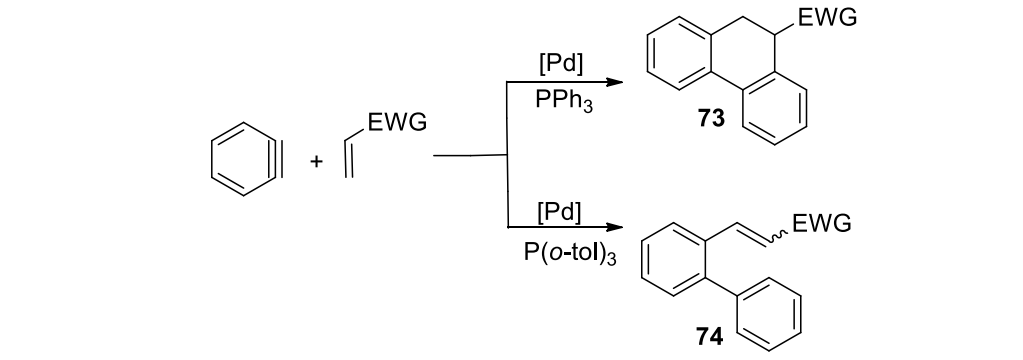


Fig. 1.4.4.3. Palladium catalysed trimerisation of arynes and alkenes.[68]

In a similar approach, Liu *et al* devised a synthesis for the fully aromatised phenanthrenes using allenes as starting materials. It was found that in not all cases the desired phenanthrene product **75** was obtained. In cases where bulky substituents

were found in R^3 and R^4, isomerisation of the intermediate was not observed and the 9,10-dihydro-9-methylenephenanthrenes **76** predominated.[69]

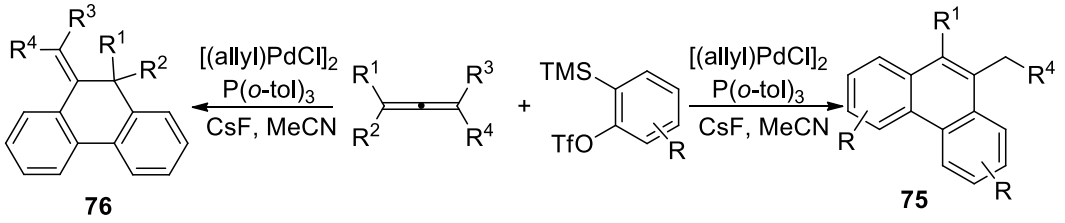


Fig. 1.4.4.4. Palladium catalysed cyclotrimerisation of arynes with allenes.[69]

1.5 The Use of Other Metal Catalysts in Aryne Chemistry

Although aryne annulations proceed predominately through palladium catalysed processes, the use of other metals for these reactions is not uncommon. Copper, nickel and gold have all been used in recent years and can provide significant advantages over their palladium counterparts.

1.5.1 A Nickel Catalysed Method for Aryne Generation

The Hu method for aryne generation through a palladium catalysed 1,2-elimination of dihaloaromatic compounds was discussed earlier in the literature review.[39-41] Recently, Cheng *et al* published a similar method which instead uses a Nickel source for catalysis. He utilises this method to generate naphthalenes through a [2+2+2] cyloaddition of benzyne with alkynes.[70]

The mechanism for the two reactions is very similar. However, Cheng and co-workers found that in order for the reaction to proceed, the nickel catalyst had to be reduced in the process. To accomplish this, stoichiometric quantities of zinc are required as a reductant.

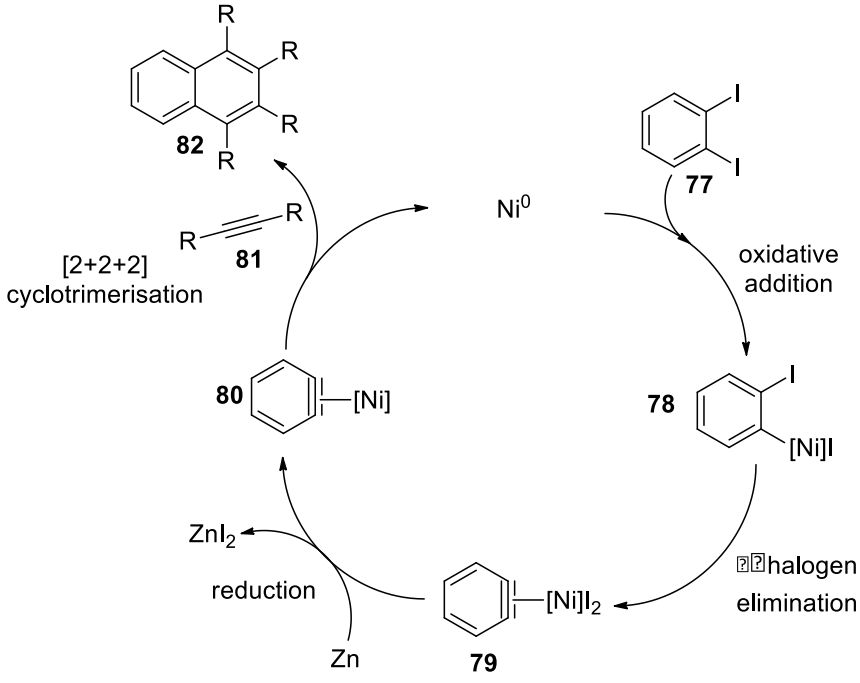


Fig. 1.5.1.1. Catalytic cycle for the nickel catalysed formation of benzyne from dihaloaromatics.

1.5.2 Three Component Couplings of Benzyne

In addition to their work on palladium catalysed TCCs, Cheng *et al* also broadened the scope of their research to include other metal catalysts. The first of two papers in this field describes the use of Nickel to catalyse a three-component coupling of arynes, enones and organoboronic acids.[71]

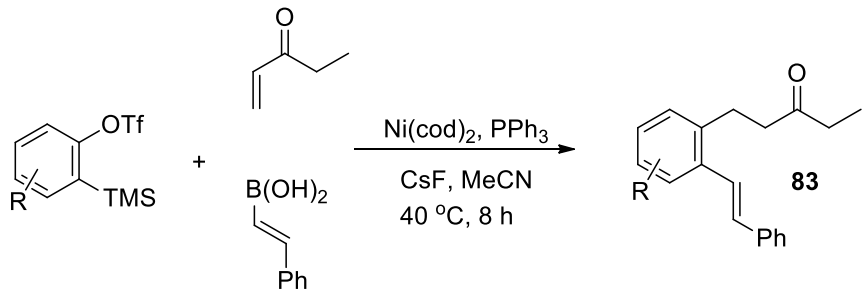


Fig. 1.5.2.1. The nickel catalysed TCC of arynes, enones and organoboronic acids.

The organoboronic acid is crucial to the process, having a dual role in the reaction mechanism. It acts as both a proton source – protonating intermediate **84** in the reaction cycle – and as a carbon nucleophile (see figure 1.5.2.2.).

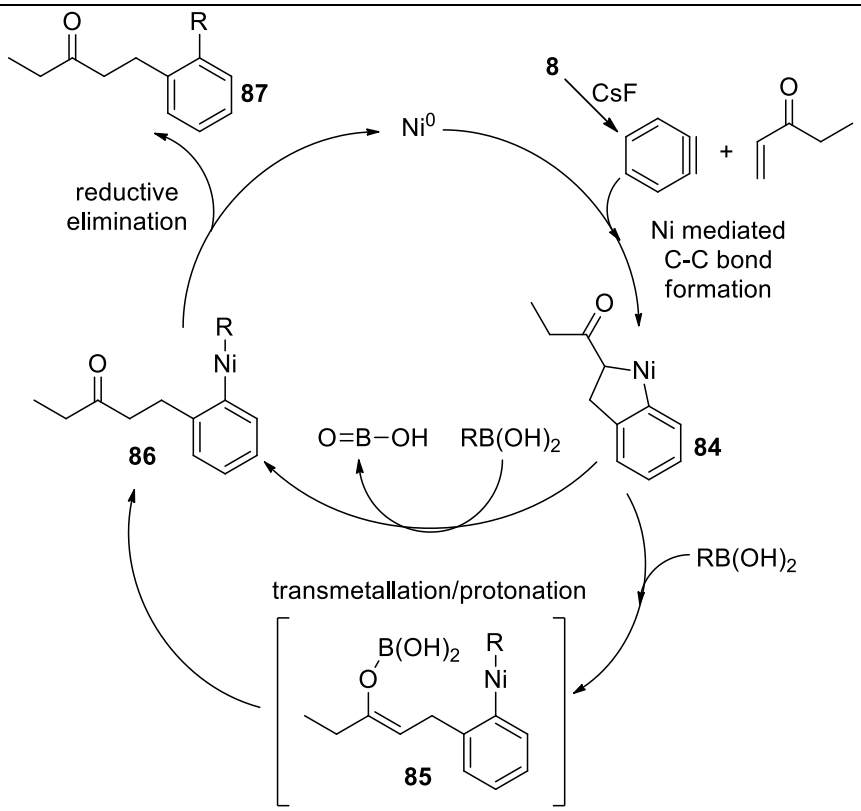


Fig. 1.5.2.2. Proposed catalytic cycle for the nickel catalysed TCC of arynes, enones and organoboronic acids.

The second article published by the Cheng group detailed their research into TCCs of arynes with terminal alkynes and activated alkenes.[72] In this instance, copper catalysis is used to promote the process through the formation of an organocuprate reagent with a terminal alkyne. This species is then reacted with an aryne to give the organocuprate intermediate **88**. This intermediate then undergoes a conjugate addition with the activated olefin to furnish products of the type **89** (see figure 1.5.2.3).

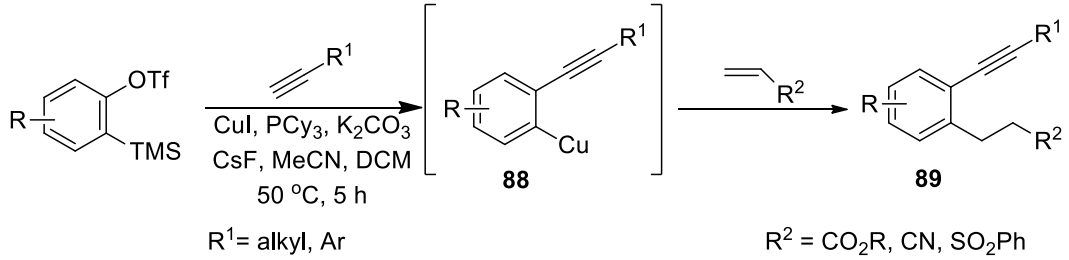


Fig. 1.5.2.3. The three component coupling of arynes, terminal alkynes and activated alkenes.[72]

The third example of an aryne TCC utilising metals other than palladium also uses copper catalysis in a very similar process to that described above. Zhang and co-workers report the three component coupling reaction of arynes, alkynes and allylic chlorides using copper catalysis (figure 1.5.2.4.).[73]

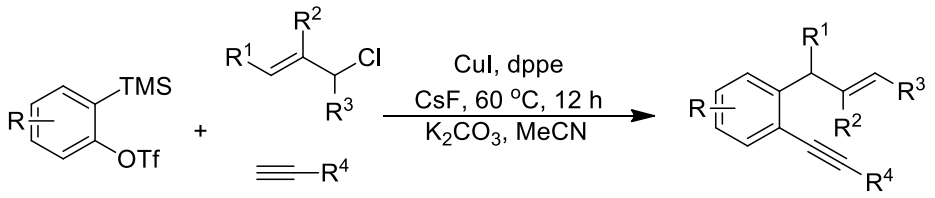


Fig. 1.5.2.4. Copper promoted coupling of arynes, alkynes and alkenes.[73]

The last example of this series utilises both copper and gold catalysis when coupling arynes with terminal alkynes. In this example, however, the terminal electrophile in the reaction is another molecule of benzyne, furnishing biphenyl derivatives as products (figure 1.5.2.5.).[74]

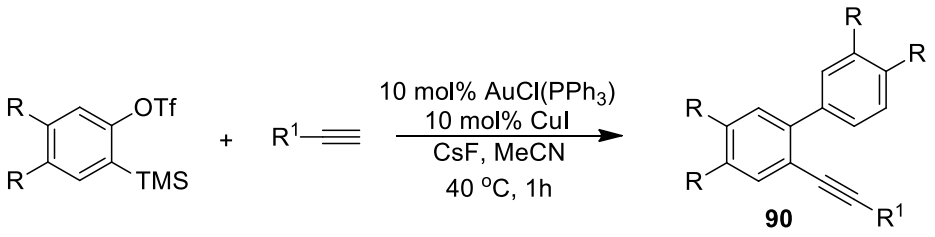


Fig. 1.5.2.5. A copper and gold catalysed aryne, aryne, alkyne TCC.

With respect to the copper, the proposed reaction mechanism proceeds in a similar fashion to those described earlier (figure 1.5.2.6.). The organocuprate intermediate **91** is formed in the first instance, which – through benzyne insertion – furnishes intermediate **92**. With respect to the gold, the first step in the reaction is the association of the catalyst with benzyne to form intermediate **93**. Subsequent nucleophilic addition of the organocuprate intermediate **91** yields the intermediate **94**, which undergoes protodemetallation to liberate the product **95**.

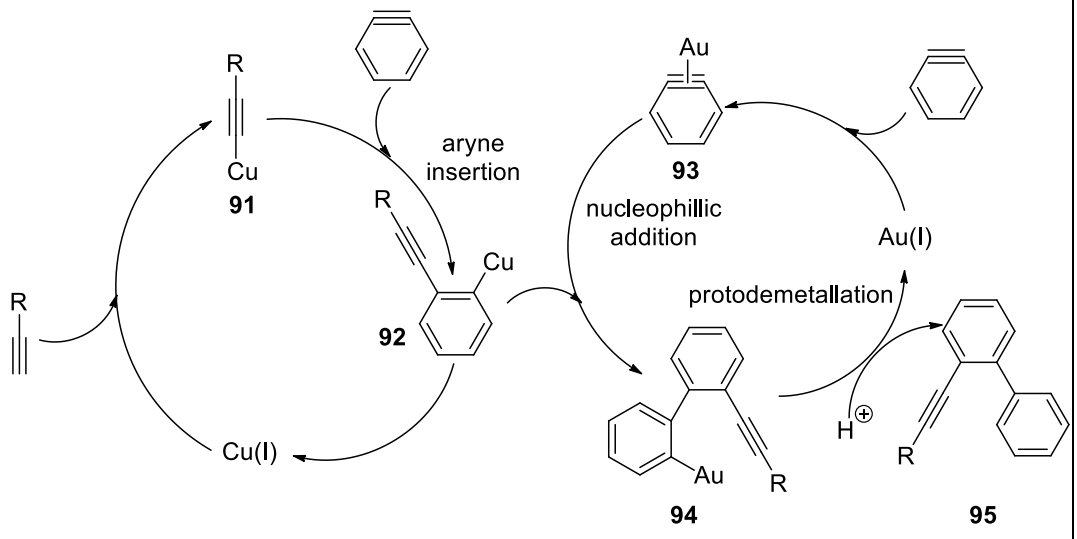


Fig. 1.5.2.6. The mechanism for the copper and gold catalysed aryne, aryne, alkyne TCC.

The reaction yields the biphenylated products in good to very good yields and is one of only a few examples combining gold catalysis with aryne chemistry.[74]

1.5.3 Metal Mediated Nucleophilic Additions to Arynes.

It is well documented that benzyne is an excellent electrophile and this trait has been exploited in many of the applications of this reactive intermediate. In recent years, the ability to form benzyne under catalytic organometallic conditions has allowed for the development of various metal mediated nucleophilic additions to the species. One such example of this is the copper mediated nucleophilic addition of terminal alkynes to arynes. This process was researched by the Zhang group and was developed with the intention of applying it to the TCC process described in figure 1.5.2.4 previously. The mechanism proceeds through an alkynyl cuprate intermediate and gives high yields of the arylated alkyne.[73]

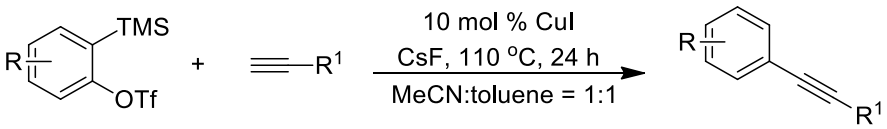
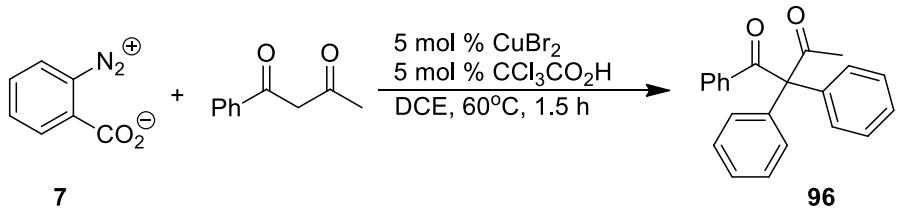


Fig. 1.5.3.1. The copper mediated nucleophilic addition of terminal alkynes to arynes.[73]

This process was further improved upon by Biehl and co-workers in 2009 when microwave conditions were applied to the reaction. Reaction times could be reduced from 24 hours to just 30 minutes in the first recorded example of microwave-assisted benzyne chemistry.[75]

The last example of a metal mediated nucleophilic addition to benzyne again utilises copper catalysis to promote the transformation. In this instance however, 1,3-diones are employed as the nucleophile and benzene-diazonium-2-carboxylate **7** is used as the benzyne precursor. It is thought that the copper catalyses the reaction by promoting the formation of the enol; this allows for the reaction of two equivalents of benzyne with the substrate, giving diphenylated products of the type **96**.[76]

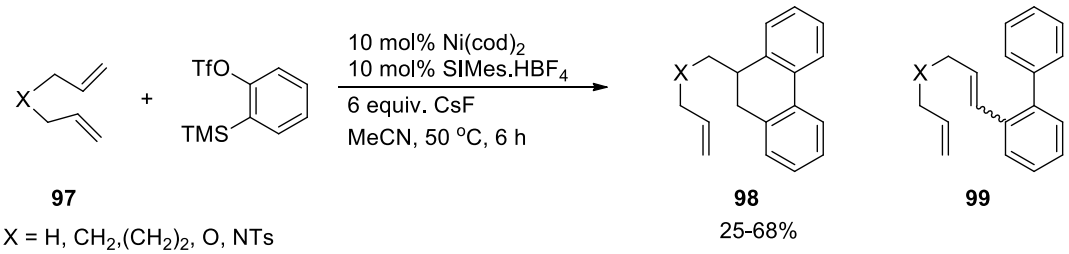


7 **96**

Fig. 1.5.3.2. Copper catalysed diarylation of 1,3-diones using benzyne.[76]

1.5.4 A Nickel Catalysed [2+2+2] Cycloaddition

Recent research into [2+2+2] cycloadditions has shown that these reactions can also be promoted using nickel catalysis. The Sato group investigated the trimerisation of 2 molecules of benzyne with an unactivated alkene. The aim of the methodology was to produce 9,10-dihydrophenanthrene derivatives – the skeletons of which feature prominently in many biologically active natural products. Upon completion of the research, it was found that 9,10-dihydrophenanthrenes of the sort **98** could be furnished from the reaction of benzyne with alkenes of the type **97**. The reaction uses a nickel catalyst with carbene ligand and furnishes the products in moderate yields. The efficiency of this reaction was somewhat limited due to the formation of the by-products **99**, and gives yields of only 25–68%.



97 **98** **99**

X = H, CH_2,$(CH_2)_2$, O, NTs

25-68%

Fig. 1.5.4.1. Nickel catalysed [2+2+2] cycloaddition of arynes and an unactivated alkene.

1.6 Conclusion

Over the past 4 years there has been significant activity in the coupling of transition metal catalysed chemistry with that of arynes. This chemistry has focussed mainly on combining aryne chemistry with that of palladium catalysed processes, but we have seen an appreciable use of other transition metal catalysed methods. Nickel, copper, and gold have all been used in conjunction with aryne chemistry and are reasonable alternatives to palladium.

The use of metal catalysis in aryne chemistry has allowed for the development of a vast new field of C–C bond forming reactions. Nucleophilic additions, aryne annulations and [2+2+2] cycloadditions have all benefitted from research in this area. By far the most prominent method developed however, is that of aryne three component couplings. Methods developed which can *ortho*-difunctionalise aromatic rings, with 2 separate substrates in one reaction are incredibly useful, and significantly add to the organic chemist's arsenal.

The discovery of *ortho*-trimethylsilylphenyl triflate as a benzyne precursor has allowed this research to flourish and its contributions to aryne chemistry are of fundamental importance. Its use however, does have some drawbacks – the lack of commercially available precursors, and the expense involved in their synthesis, is a problem that must be addressed in order for aryne chemistry to continue to flourish. As a result, there is significant ongoing research into developing new methods of generating benzyne from cheap, readily available starting materials which are compatible with organometallic catalysed processes. This field of research is particularly important in the Greaney group due to the experiences gained whilst working on aryne chemistry, and features prominently in the research in this thesis.

2 The Benzyne Aza-Claisen Reaction

This project arises from some interesting results obtained from an attempt at three component coupling utilising benzyne and a Buchwald reaction. All attempts at this TCC were performed by Jacyln Henderson who was a previous member in the group.[77] The reaction was found to be unsuccessful due to the nucleophilicity of the amine species. The process would not work giving none of the desired product **100a**. It was found that benzyne could not undergo carbopalladation under these conditions, instead reacting directly with the amine to produce *N*-phenylated amines **100b** as the sole products for the reaction.

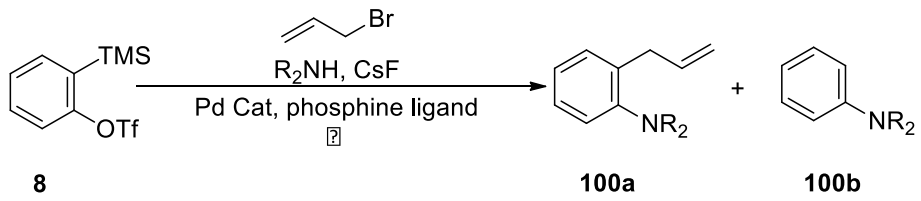


Fig. 2.1. A three component Buchwald coupling of benzyne, allyl bromide and amines.

It was decided to explore this reaction with benzyne in the hope of discovering some new and novel chemistry. Although nucleophilic addition to benzyne was well known in the literature,[3, 9, 25, 26] it was thought that Jaclyn might be able to add to this class of reactions by making use of the ylide formed in the addition process. It was hypothesised that if a tertiary amine was reacted with benzyne, then the arene ylide intermediate **101** would be produced; this ylide could then rearrange to give the disubstituted aromatic product **102** (see figure 2.2.). The use of this ylide intermediate for rearrangement has been reported substantially in the literature,[78-85] but never with a tertiary amine. It was hoped that this work would add to the still growing field of aryne chemistry, and would provide a new route for the synthesis of *ortho*-substituted aniline derivatives.

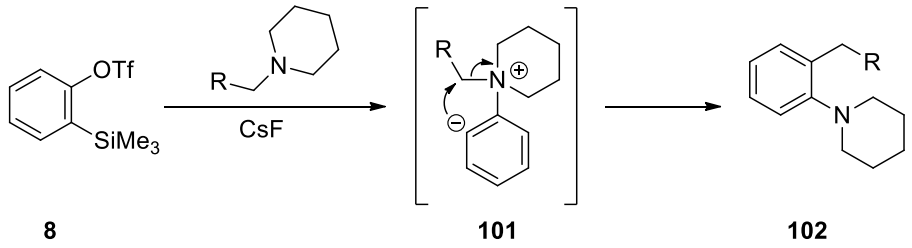


Fig. 2.2. Reaction of benzyne with a tertiary amine.

Unfortunately, upon investigation, this reaction was found to be unsuccessful with no rearranged products isolated from the reaction mixture. It was determined that this may be due to the proposed rearrangement proceeding *via* a 4-*endo*-tet transition state which is disfavoured by Baldwin's rules. In order to overcome this problem, a new system had to be devised which obeyed the rules set out by Baldwin, and at the same time was still in line with the methodology we were trying to develop.

The solution was to append an allyl group to the amine. This would allow the reaction to proceed *via* a 6-*endo*-trig transition state after reacting with benzyne, and would still give disubstituted aniline products.

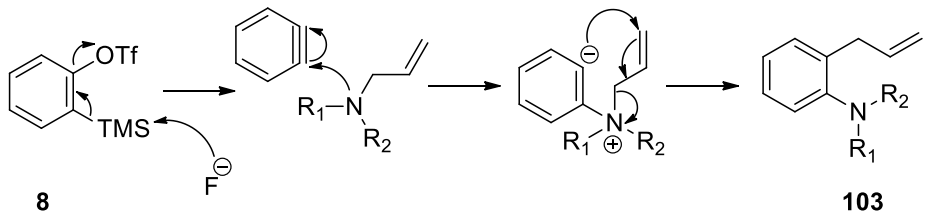


Fig. 1.5.2. The hypothesised reaction of benzyne with a tertiary allyl amine going *via* a 6-*endo*-trig S_N2' mechansim.

On consultation of the literature, it was found that similar work had been performed in the past with alkynes. Vernon[86] and others[87] reacted tertiary allylic amines **104** and their derivatives, with activated alkynes such as dimethylacetylenedicarboxylate (DMAD) **105** at room temperature to give fully substituted olefin products.

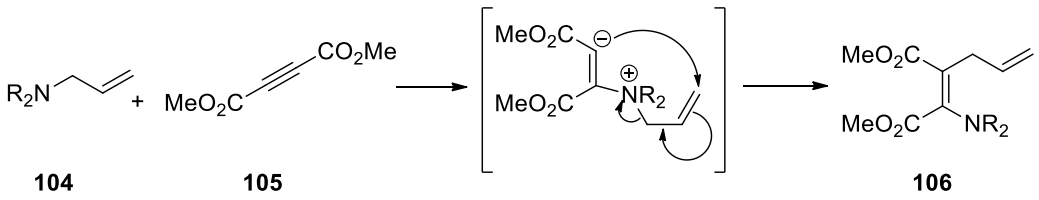


Fig. 1.5.3. The precedent for the benzyne aza-Claisen reaction.

Interestingly, Vernon tried to apply his methodology with arynes, using benzenediazonium-2-carboxylate **7** as the benzyne precursor. Unfortunately under his conditions none of the desired product was produced.

2.1 Reaction Optimisation

The majority of the reaction optimisation for this reaction was carried out by Guillaum Bertrand- a project student under the supervision of Jaclyn Henderson. My contributions consisted of the development of those conditions to make the procedure as reproducible as possible. All exploration of substrate scope and all subsequent work completed on this project was performed by me.

It was soon found that the benzyne aza-Claisen reaction was not to proceed as planned. Using conditions similar to those published by Vernon on his work with alkynes, none of the *ortho*-substituted aniline products could be obtained. It was found that when *N*-allylpiperidene **107**, benzyne precursor **8** and caesium fluoride were stirred together in acetonitrile at room temperature, that significant amounts of a very polar compound was formed. This product was isolated and was found to be the tertiary allyl amine salt **108a**. It was apparent that the anion of the zwitterionic species was being protonated, and after investigation using deuterated solvents, it was found that acetonitrile was the proton source. Numerous experiments were performed using aprotic solvents, ionic solvents and adding metal salts in the hope that the zwitterion could be preserved in order to undergo the S_N2' rearrangement. Unfortunately in all cases the reaction either yielded the tertiary amine salt or no product at all.

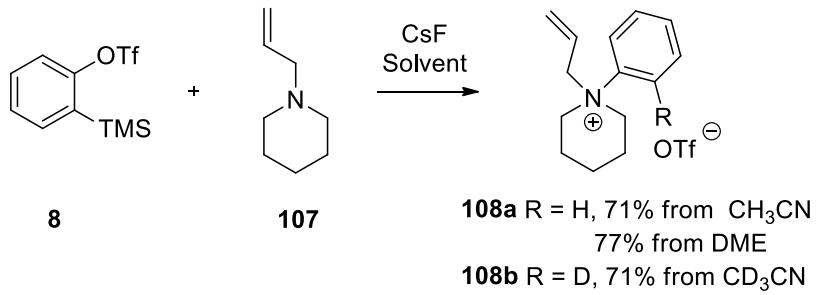


Fig. 2.1.1. The reaction of benzyne with *N*-allylpiperidine at room temperature.

Having developed a suitable protocol for making tertiary allyl amine salts, we examined the literature[88-92] and decided that these compounds might actually be activated for an aza-Claisen (or 3-aza-Cope) rearrangement (see figure 2.1.2.).

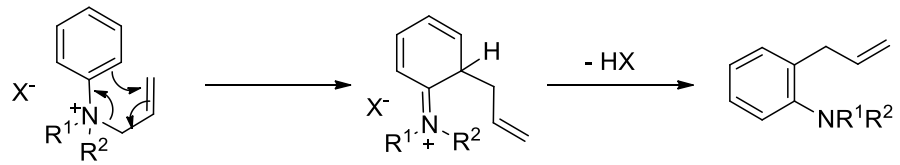


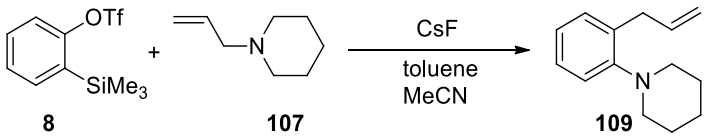
Fig. 2.1.2. The charge accelerated aza-Claisen rearrangement.

The aza-Claisen (or 3-aza-Cope) reaction of allyl enamines is a powerful, atom-efficient method for functionalised amine synthesis. The scope of the reaction, however, has yet to be fully realised due to the forcing conditions necessary to achieve rearrangement. In its simplest form, the rearrangement of allyl enamines requires very high reaction temperatures (>200 ºC) and is seldom used as a preparative method. Charge-accelerated aza-Claisen rearrangements, however, take place under milder reaction conditions and have been widely studied in terms of substrate range,[89, 90, 93] stereocontrol,[91, 94, 95] and application to complex molecule synthesis.[89, 90] The basic nitrogen atom provides the site for charge acceleration, usually *via* protonation,[88] quaternization[89, 91, 92] or Lewis acid coordination.[88] Even so, simple allylaniline aza-Claisen reactions require stoichiometric amounts of Lewis acids such as $BF_3.OEt_2$ and reaction temperatures well in excess of 100 ºC.[91]

By means of reacting benzyne with tertiary allyl amines we had developed a new protocol for achieving the starting materials required for a charged accelerated aza-

Claisen rearrangement. It was therefore only logical that we should try and combine the two processes into a one pot reaction, in the hope that with some extra heating, we could achieve both the nucleophilic addition and the rearrangement. This would allow us to access the originally desired *ortho*-functionalised anilines in one step.

With this in mind, a new round of reaction screening with more vigorous reaction conditions was performed. The reaction optimisation is described in table 2.1.1. below



8 **107** **109**

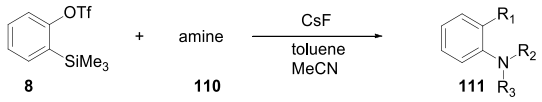
Entry	Time (h)	Ratio Toluene/MeCN	Concentration (M)	Yield
1	12	9:1	1.7	0%
2	24	1:1	0.7	25%
3	24	3:1	0.7	36%
4	48	1:1	0.5	85%
5	48	3:1	0.5	76%
6	48	4:1	0.5	52%
7[a]	48	3:1	0.5	90%
8	48	3:1	1	75%
9	48	3:1	0.25	92%

Table 2.1.1. Reactions were carried out on a 0.3 mmol scale with 1.5 equiv. allyl amine and 3 equiv. CsF at reflux in a sealed tube. [a] 1.5 equiv. benzyne precursor with 0.3 mmol amine was used.[77]

The reactions were performed using 3 equivalents of caesium fluoride as the fluoride source. It was found that the best solvent system for the reaction was a toluene/acetonitrile mixture. A balance had to be maintained between the two solvents: enough acetonitrile had to be used in order to solubilise the caesium fluoride, whereas toluene was needed to help achieve higher temperatures. The best conditions yielded 92% of **109** and are described in entry 9. A 3:1 ratio of toluene to acetonitrile refluxing for 48 h was found to be the optimum conditions.

2.2 Exploring the Scope

With a suitable set of reaction conditions in hand the substrate scope of the reaction was then explored. Firstly, the amine derivatives were investigated – the results of which are detailed in table 2.2.1.



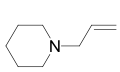
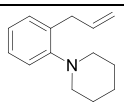
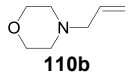
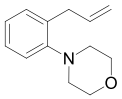
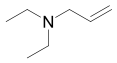
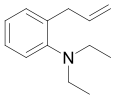
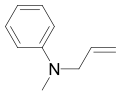
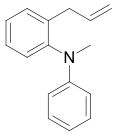
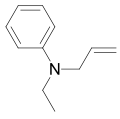
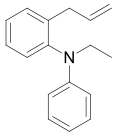
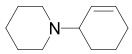
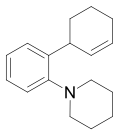
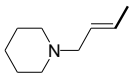
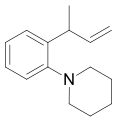
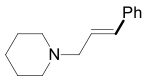
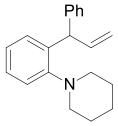
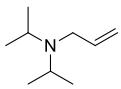
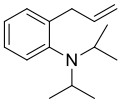
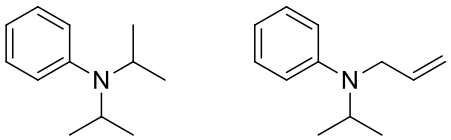
Entry	Amine	Product	Yield (%)[a]
1	 **110a**	 **111a**	92
2	 **110b**	 **111b**	62
3[b]	 **110c**	 **111c**	65
4	 **110d**	 **111d**	91
5	 **110e**	 **11e**	71
6	 **110f**	 **111f**	74
7[c]	 **110g**	 **111g**	31[b,c]
8	 **110h**	 **111h**	0
9	 **110i**	 **111i**	0[d]

Table 2.2.1. The benzyne aza-Claisen rearrangement. Conditions: *o*-trimethylsilylphenyl triflate (1 equiv), amine (1.5 equiv) and CsF (3 equiv) in toluene (2.25 mL) and MeCN (0.75 mL). Reactions were carried out on a 0.2 mmol scale and heated to 110 ºC for 48 h in a sealed tube. [a] Isolated yields. [b] Reaction was performed in refluxing DME. [c] A 50% yield of *N*-phenylpiperidine was also obtained. [d] A 34% yield of diisopropylphenylamine and 45% yield of isopropylallylphenylamine were isolated as by-products. All starting materials were made according to known literature procedures.[96]

The reaction was found to be viable for a range of simple tertiary allyl amines, with the morpholine, diethyl and aniline derivatives **111b** – **e** undergoing smooth rearrangement in good to excellent yields. Interestingly, the diisopropylallylamine derivative **110i** yielded none of the desired product; instead, a 34% yield of diisopropylphenylamine **112** and a 45% yield of isopropylallylphenylamine **113** were isolated as the sole products of the reaction. It is thought that these products are formed through a dissociative E1 mechanism where the loss of cationic allyl or isopropyl species is favoured over the aza-Claisen rearrangement.



112 **113**

Fig 2.2.1. The by-products **112** and **113** isolated from the reaction of **110i** and benzyne.

Substituted allyl substrates were next examined and it was found that *Z*-alkenes such as the cyclohexenyl amine **110f** worked well, yielding tricyclic aniline **111f** in 74% yield. However, it was found that *E*-substitution at the terminal end of the allyl group was not well tolerated. The crotyl and cinnamyl derivatives **110g** and **110h** – which are predominately *E* – yielded only 15% and 0% respectively under standard conditions. It was found that the crotyl substrate could undergo the rearrangement in the higher yield of 31% at the lower temperature of 80 ºC in refluxing DME. It is thought that the *E*-stereochemistry interferes with the aza-Claisen rearrangement through steric interactions and thus elimination mechanisms are more favored. The methyl group did serve as a marker, however. The formation of product **111g** with the methyl group in the benzylic position proves the reaction takes place *via* a 3,3-sigmatropic shift and not a possible C–N insertion process (see figure 2.2.2.).

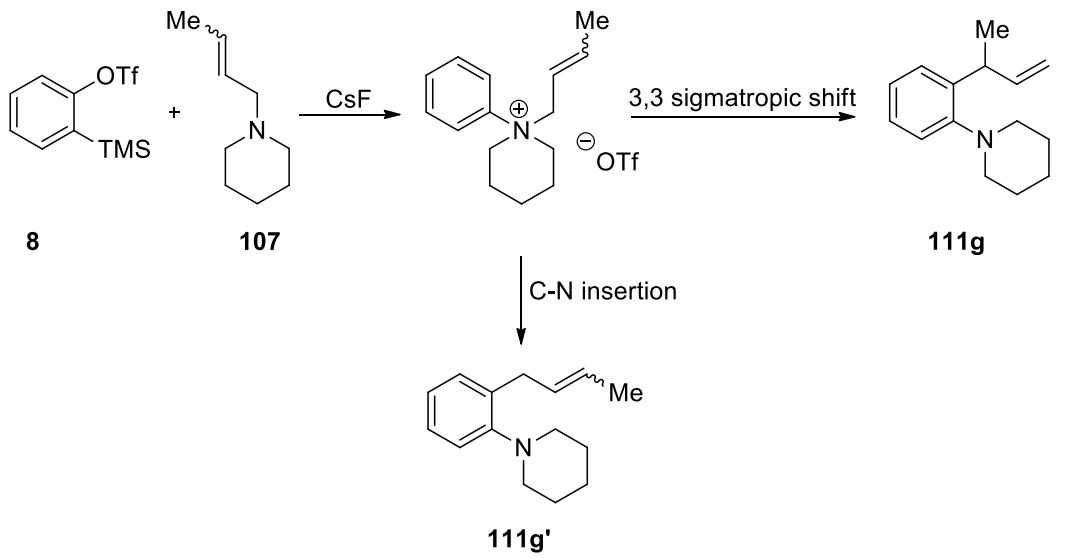


Fig 2.2.2. The formation of product **111g** over **111g'** proves a 3,3 sigmatropic shift mechanism is in progress.

When hypothesising about the mechanism of the benzyne aza-Claisen reaction, the point was raised that the allyl group could transfer intermolecularly. A crossover experiment was conducted between amines **110b** and **110f** to check this theory. The results were negative, with GC-MS analysis identifying only the expected anilines **111b** and **111f** plus a small amount of *N*-phenylmorpholine (figure 2.2.3). No crossover products could be detected indicating that the reaction did proceed *via* a 3,3-sigmatropic shift. The HPLC results for these experiments can be found in appendix A.

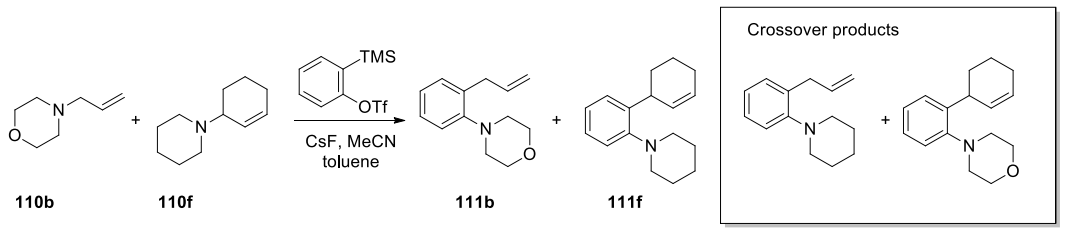


Fig 2.2.3. A crossover experiment.

The scope of the reaction with respect to aryne structure next examined. The sesamol aryne **114b** and naphthyne **114c** were both good substrates, producing the aza-Claisen products in 57% and 79% yields (Entries 1 and 2). The naphthyne substrate showed excellent regiocontrol with only one regioisomer being formed. The regioselectivity arises from the nucleophilic addition of amine occurring at the more sterically accessible *β*-position and is concurrent with previous literature.[97]

The electron rich methoxy substituted aryne substrates **114d** and **114e** (Entries 3 & 4) provided valuable insight into the mechanism of the benzyne aza-Claisen reaction. Both examples gave good yields of aza-Claisen products and in the case of the disubstituted aryne **114d**, excellent regiocontrol was observed. In both instances, the amine addition occurred exclusively *meta* to the methoxy group. This concurs with previous publications and can be attributed both to steric and electronic interactions.[9, 25, 98] The subsequent rearrangements to the *ortho*-substituted arenes however, occurred with interesting and unexpected regioselectivity. When substituted arynes are employed, it is important to note that when the tertiary amine undergoes the aza-Claisen rearrangement it has a choice of which position on the aromatic ring it can rearrange to. In the case of the monomethoxy derivative **114e**, compounds **111m** and **111m'** are produced in a 2.3:1 ratio indicating that the allyl group has a tendency to rearrange away from other substituents on the aromatic ring. Similar behaviour is observed in the case of the dimethoxy derivative **114d** where the 1,2,4,5-tetra-substituted arene is produced exclusively.

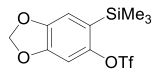
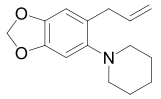
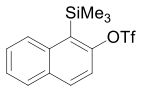
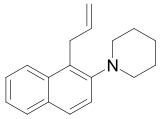
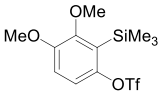
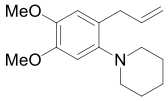
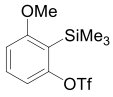
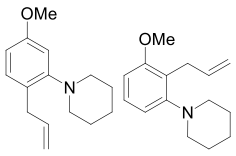
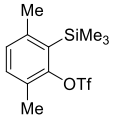
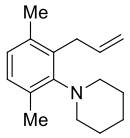
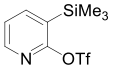
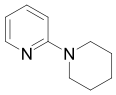
Entry	Aryne precursor	Product	Yield (%)[a]
1	 **114b**	 **111j**	57
2	 **114c**	 **111k**	79
3	 **114d**	 **111l**	76
4	 **114e**	 **111m** **111m'**	79[b]
5	 **114f**	 **111n**	15[c]
6	 **114g**	 **111o**	40

Table 2.2.2. Reaction conditions: aryne precursor (1 equiv.), 1-allylpiperidine (1.5 equiv.) and CsF (3 equiv.) in toluene (2.25 mL) and MeCN (0.75 mL). Reactions were carried out on a 0.2 mmol scale and refluxed for 48 h in a sealed tube. [a] Isolated yields. [b] Products isolated as a 2.3 : 1 ratio of **111m** : **111m'**. [c] A 25% yield of the de-allylation product was obtained. All starting materials were made according to known literature procedures.[17, 35, 99]

One example which didn't work very well was the dimethyl derivative **114f**. A 15% yield of **111n** was obtained with an additional 25% of the deallylation product. The low yields are thought to be due to steric hindrance during both the nucleophilic addition and the rearrangement. The 2,3-pyridyne precursor **114g** was not viable in the reaction; initial nucleophilic addition of the amine was observed, but the subsequent aza-Claisen rearrangement did not take place under the reaction conditions. Rather, de-allylation occurred and a moderate yield of 2-(piperidin-1-

yl)pyridine **111o** was isolated after 48 h. It was thought that the electron deficiency of the pyridine reduced the facility of the aromatic electrons to take part in the aza-Claisen rearrangement.

In line with the previous work employed on the DMAD alkyne substrates,[87] we further explored the scope of the reaction employing cyclic tertiary amines of the type **115**. By including the allyl group as part of the heterocycle we can induce a ring expansion to generate medium sized benzannulated heterocycles such as **116** in 1 step (figure 2.2.4.).

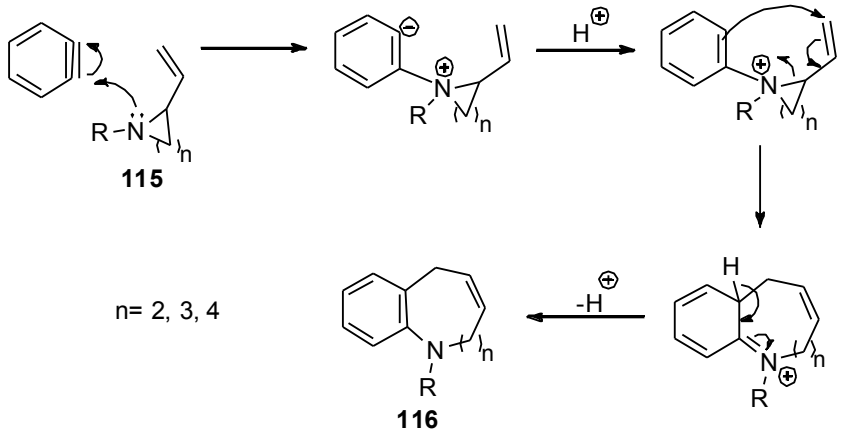
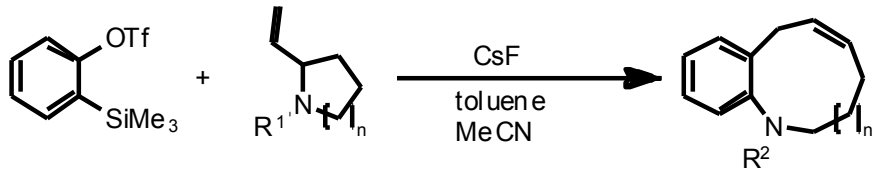


Fig. 2.2.4. The formation of benazannulated heterocycles from *α*-vinyl amines acting on benzyne.

The reaction was first employed using the 5-membered pyrrolidine and 6-membered piperidine derivatives. The results of which are detailed in table 2.2.3.

The pyrrolidine derivatives worked well giving moderate yields (25 – 41%) of the 9-membered ring products (entries 1 – 4). The magnitude of the alkene C–H coupling constants (ca. 8 Hz) indicated that the *Z*-stereoisomers had been formed in each case. Interestingly, this was contrary to that observed in the DMAD system where only the *E*-stereoisomers were isolated.[87] The piperidine derivatives worked slightly less well, purification by chromatography yielded pure product for entry 6 only. Entries 5 & 7 contained impurities similar in structure to the desired compound which could not be removed. These impurities could be decomposition products – previously observed in

these kinds of systems – or possibly some of the *E*-stereoisomer. These compounds were not published in the communication due to their impure nature.



8 **115** **116**

Entry	Product	n	R^1	R^2	Yield (%)[a]
1	**116a**	1	Me	Me	41
2	**116b**	1	Bn	Bn	30
3	**116c**	1	Ph	Ph	25
4	**116c**	1	H[b]	Ph	40
5	**116d**	2	Me	Me	37
6	**116e**	2	Bn	Bn	28
7	**116e**	2	H[b]	Ph	51

Table 2.2.3. Reaction conditions: *o*-trimethylsilylphenyl triflate **8** (1 equiv.), amine (1.5 equiv.) and CsF (3 equiv.) in toluene (2.25 mL) and MeCN (0.75 mL). Reactions were carried out on a 0.2 mmol scale and were stirred for 24 h at RT and then refluxed for 48 h in a sealed tube. [a] Isolated yields. [b] 2 equiv of *o*-trimethylsilylphenyl triflate **8** to 1 equiv. amine was used.

Interestingly, secondary amines could be employed in these systems. It was possible in the case of entries 4 and 7 to start with the secondary amine and generate the tertiary amine *in situ* using two equivalents of benzyne precursor; these products then rearranged to the *N*-phenyl heterocyclic products in good yields.

With the 5 & 6-membered rings working well, we turned our attention to the 4-membered azetidine derivatives. When 1-methyl-2-vinyl azetidine **117** was reacted with benzyne at 110 °C for 48 h, none of the rearranged product was observed. Instead, the reaction halted after the nucleophilic addition leaving the tertiary amine

salt **118** as the major product. This may be attributed to the simple geometry of the system, with the substituents not being in the correct orientation for the aza-Claisen rearrangement to proceed.

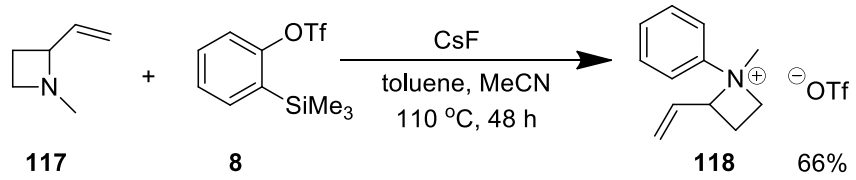


Fig. 2.2.5. The reaction of 1-methyl-2-vinylazetidine with benzyne.

At this point the results were compiled for publication; however, under a more thorough scrutiny of the literature it was noted that similar chemistry had been performed almost 50 years previously. Wittig and co-workers had investigated the Diels-Alder reaction of *N*-methylpyrrole with benzyne and found that carbazole product **121** was unexpectedly formed in 12% yield. The reaction proceeded at room temperature, *via* a Diels-Alder reaction, followed by an S_N2' addition. This example was particularly interesting as the low temperatures indicate that the reaction proceeded through the S_N2' mechanism which we had attempted originally (see figure 2.2.6.).[10]

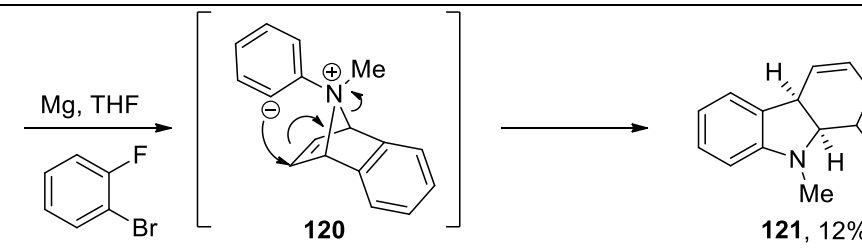


Fig. 2.2.6. The reaction of *N*-methylpyrrole with *o*-fluorobromobenezene *via* a benzyne mechanism.

Enthused at the prospect of applying our newer and more efficient method of generating benzyne to this reaction system, we proceeded to attempt the reaction using the benzyne precursor **8**. Unfortunately, the reaction yielded us none of the desired semicarbazole product. Interestingly however, we did achieve a 66% yield of the unexpected naphthalene product **123**. We believe the key step in this transformation follows the formation of the zwitterion **120**. Under Wittig's strongly basic conditions, the anion in the zwitterion is retained and the reaction can proceed

via the S_N2' pathway. Under our conditions, this anion is protonated giving us intermediate **122.** This intermediate cannot continue through the S_N2' pathway and is instead deprotonated at the bridgehead position. This is then followed by aromatisation to give the naphthalene product **123**.

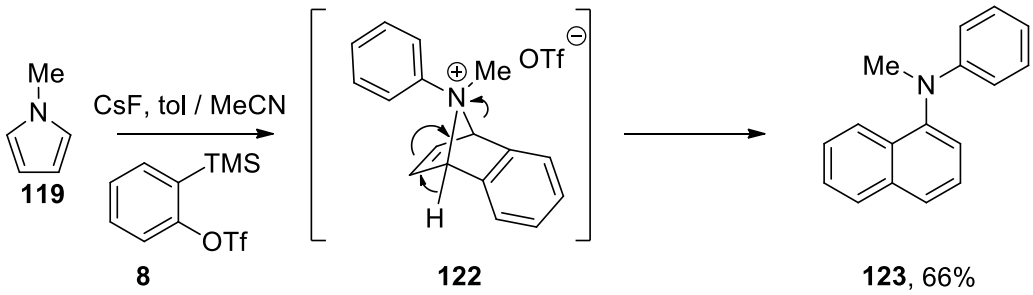


Fig. 2.2.7. The reaction of *N*-methylpyrrole with benzyne precurser **8** to give napthalene product **123**.

The results of these two experiments were fundamentally quite interesting. The fact that two different reaction pathways can occur – dependant on which method of benzyne production was employed – was an interesting outcome. Further work was completed trying to investigate whether the S_N2' pathway could be promoted in other systems at room temperature using *o*-fluorobromobenezene as the benzyne precursor. It was found, however, that the reaction did not proceed with any other tertiary allyl amine derivatives and that the reaction was specific to *N*-methylpyrrole.

2.3 Side Reactions

Most of the above examples were encumbered by side reactions which diminished the yield considerably. As a case study, the side-reactions when allylmorpholine is reacted with benzyne will be discussed. Figure 2.3.1 shows the products obtained from the reaction.

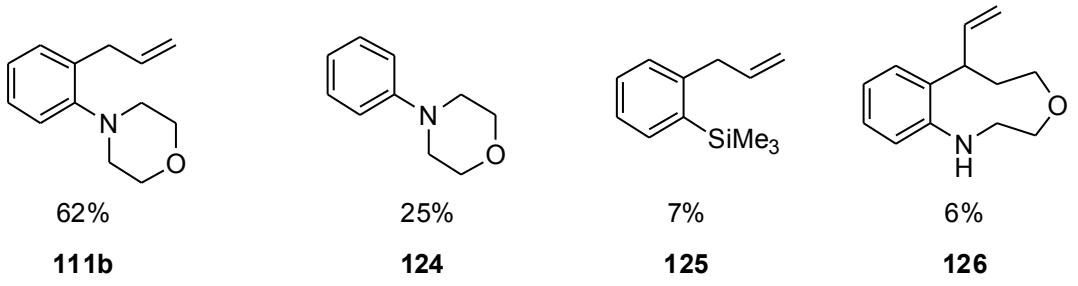


Fig. 2.3.1. The products arising from the reaction of allyl morpholine with benzyne.

The main by-product for almost all of the examples in this series is the phenyl substituted amine. In this case, the yield of the 1-phenyl-morpholine **124** is particularly large at 25%. It is hypothesised that this product arises from the dissociation of the allyl group from the cationic intermediate as illustrated in figure 2.3.2.

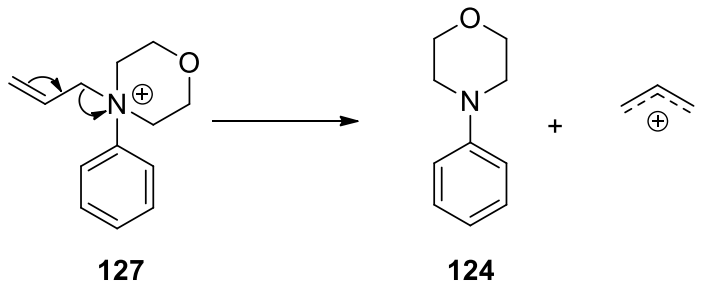


Fig. 2.3.2. Mechanism for the formation of by-product **124.**

An unusual by-product found commonly in lower yields in these reactions is compound **125**. In a lower yield of only 7% this product probably arises from an electrophilic aromatic substitution. The mechanism for the formation of this by-product has as yet not been elucidated.

A hypothesised product which is specific to this allyl morpholine derivative is compound **126**. Spectroscopic evidence had shown that a single proton was present in the benzylic position indicating that there was an unexpected substituent on this atom. It is believed that this substitution pattern may be formed *via* a rearrangement of product **111b**. The benzylic position is suitably acidic to allow deprotonation, and the resulting anion could induce a 1,3-shift to generate the heterocyclic product **126** (figure 2.3.3.). Due to minute quantities of this material being isolated, full

characterisation could not be achieved, but mass spectrometry, proton NMR and carbon NMR all support this theory.

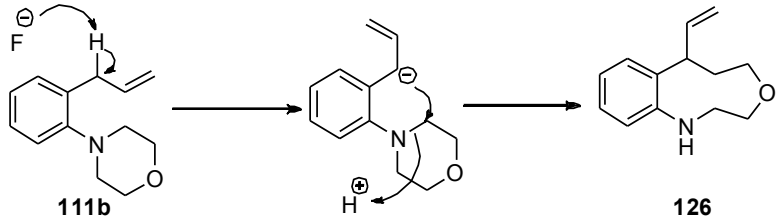


Fig. 2.3.3. Mechanism for the formation of by-product **126**.

2.4 Possible Extensions of Chemistry

2.4.1 Exploring Other Substrates

Having achieved tremendous success with the reaction of tertiary allyl amines with benzyne in the benzyne aza-Claisen reaction, it was only logical to explore the scope of other heteroatoms in the process. With this in mind, the reaction utilising allyl ethers and allyl thioethers was also explored. We were optimistic about the oxygen and sulfur derivatives of the reaction as the respective 3,3-sigmatropic shifts occur at temperatures far lower than the charge accelerated aza-Claisen rearrangement. This reaction would generate products of the type **126** and was an obvious extension of the methodology that needed to be investigated.

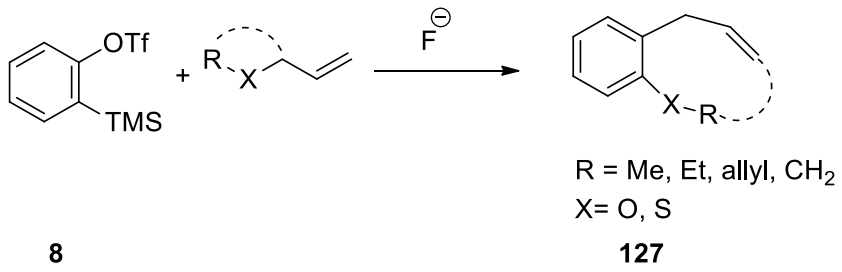


Fig. 2.4.1.1. The reaction of benzyne with allyl ethers, vinyl epoxides and allyl thioethers.

A variety of different allyl ethers and vinyl epoxides were employed in the hope of inducing a benzyne-Cope rearrangement. The reaction was initially tried under the conditions developed for the benzyne aza-Claisen reaction but was found to be very messy and no allylic protons could be observed in the crude NMR. Temperature, solvent and fluoride sources were all varied in the screening process but regrettably this reaction was found to be unsuccessful. It is thought that the zwitterionic species generated in this process would not have the same stability as its amino counterpart and would therefore undergo decomposition instead of the rearrangement.

The thioether derivatives were attempted by another member of the group – Kallolmay Biswas. Kallolmay tried a variety of different allyl thioethers under a range of different conditions, but quickly found that the sole products for these reactions were the allylic dissociation products.

2.4.2 Novel Reactions With Propan-2-one Derivatives

Further exploring the applicability of our methodology to other systems, it was decided to investigate the possibility of replacing the allyl group with a propan-2-one group. The first novel reactions of this class involved reacting propan-2-one derivatives **128** and **129** with benzyne. It was hoped that these compounds would follow a similar reaction mechanism to that of the benzyne aza-Claisen reaction and would give the vinylic ethers **130** and **131** as depicted in figure 2.4.2.1.

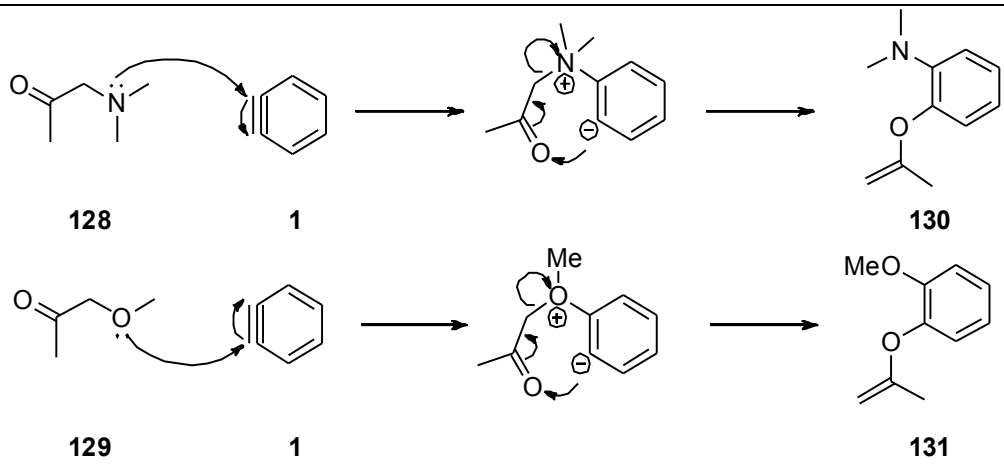
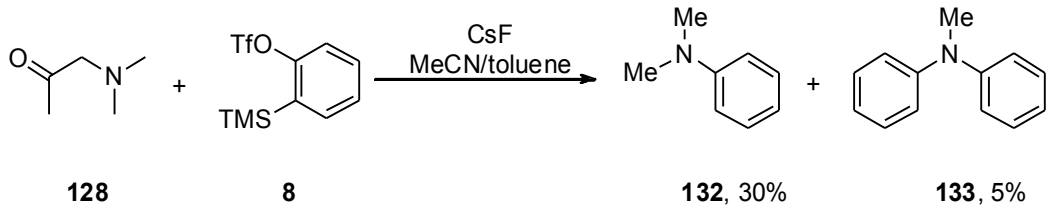


Fig. 2.4.2.1. Novel reactions with propan-2-one derivatives.

Unfortunately, when these reactions were performed, no product was observed. Interestingly, in the case of the amino derivative **128**, 30% of *N*,*N*-dimethyl aniline **132** and 5% of *N*,*N*,-diphenylmethylamine **133** were recovered. This indicated that the amines were performing the nucleophilic attack as in the original experiment, but the rearrangement was not occurring. The propan-2-one group was dissociating in a similar fashion as observed with the benzyne aza-Claisen reaction.

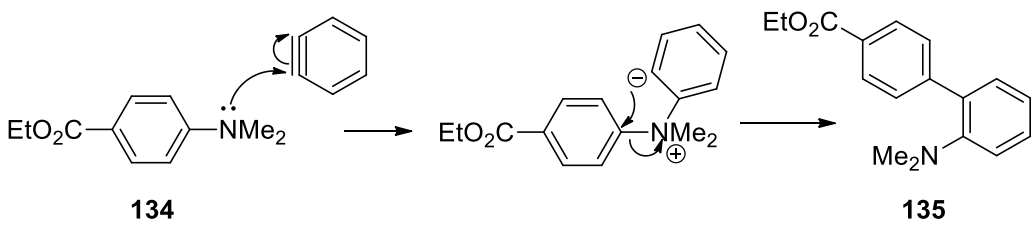


128 **8** **132**, 30% **133**, 5%

Fig. 2.4.2.2. The formation of by-products dimethylaniline **132** and *N,N*,diphenylmethylamine **133**.

2.4.3 A 1,3-Sigmatropic Shift

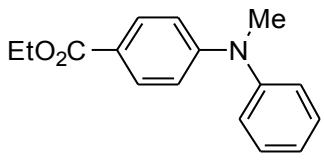
Another reaction which was attempted was the reaction between ethyl-4-dimethylaminobenzoate **134** and benzyne. It was decided to revisit the Hoffmann rearrangement to ascertain for ourselves that this reaction was not feasible. In order to do this, we appended an ester group to an aniline in the hope that the electron withdrawing effect would aid the reaction. We performed the reaction under the standard conditions developed for the tertiary allyl amines, and it was hoped that a 1,3-sigmatropic shift would occur after the addition of the amine. This would give the dimethylaniline derivative **135** as depicted in figure 2.4.3.1.



134 **135**

Fig. 2.4.3.1. The reaction of ethyl-4-dimethylaminobenzoate with benzyne.

Unfortunately, this reaction yielded similar results to that carried out with the propan-2-one substrates. A 59% of the aniline **136** was obtained indicating that the addition of the amine proceeded well, but the elimination of the methyl group was more favourable than the rearrangement.

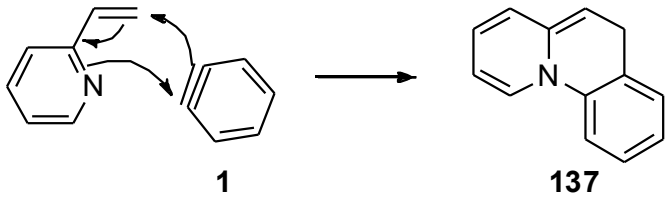


136, 59%

Fig. 2.4.3.2. An aniline by-product.

2.4.4 A Diels-Alder Reaction With 2-Vinylpyridine

When hypothesising which tertiary allyl amines would be interesting to react with benzyne, 2-vinylpyridine was discussed. After some consideration, it was decided that 2-vinylpyridine would not react in the same way as the tertiary allyl amines but might in fact undergo a Diels-Alder reaction with benzyne. Although this reaction was not directly related to the project the group was currently undertaking, the unusual heterocyclic product **137** (see figure 2.4.4.1.) was interesting enough to warrant a few trial reactions.



1 **137**

Fig. 2.4.4.1. The proposed reaction between 2-vinylpyridine and benzyne.

A few trial reactions were performed under the conditions developed for the benzyne aza-Claisen reaction and the temperature was varied from room temperature to 110°C. Unfortuantely these reactions gave complex mixtures of unidentifiable products and were not further pursued.

2.5 Conclusions

It can be concluded that the nucleophilic addition of tertiary allyl amines to benzyne followed by an aza-Claisen rearrangement can be performed in an easy one-step process for simple reactants. Steric hindrance plays an important role and it was found that in both the nucleophilic addition and the rearrangement, steric interactions affected the yield dramatically.

This procedure was also employed in the synthesis of medium to large sized rings. The yields for this process were moderate to poor and it is believed that this may be due to the product decomposition described in other, similar reports of ring expansion methodologies.

The attempt to improve on the synthetic methodology presented by Wittig *et al*, on the formation of semicarbazoles from the reaction of benzyne with *N*-methylproline, was found to be unsuccessful. We did, however, manage to generate appreciable yields of a different naphthalene product providing us with valuable insight into the reaction system.

Disappointingly, all other efforts to expand the scope of the reaction were found to be unsuccessful. Allyl ethers, allyl thioethers and propan-2-one derivatives were all found not to be viable in the reaction.

Overall this chemistry was deemed successful and was considered to be a valuable addition to the field of aryne chemistry. The results were compiled and accepted in the journal Angewandte Chemie International Edition for publication.[100]

3 The Generation of Benzyne From Benzoic Acid Using C–H Activation

The *o*-triflatosilane benzyne precursors are an excellent set of compounds that can generate benzyne mildly, using innocuous reagents and in excellent yields. Furthermore, their discovery has single-handedly allowed the use of arynes in transition metal catalysed methodology. Our use of *o*-trimethylsilylphenyltrifluoromethane sulfonate **8** and its derivatives in the benzyne aza-Claisen reaction proved incredibly successful, and there are many positive aspects concerning this methodology. However, during our research into the benzyne aza-Claisen reaction, we did find one major drawback to their use – the availability of precursors. Although the simplest precursor **8** is commercially available from Sigma-Aldrich, it is rather expensive at about £15/g. In addition to this, the derivatives are not commercially available and must be synthesised in several steps and at great expense in the laboratory. What is required is a method for generating benzyne from cheap, readily available starting materials which is compatible with transition metal catalysed chemistry.

With this in mind, we began our search into developing a new and novel methodology for the generation of benzyne. After researching areas in both aryne chemistry and C–H activation, we devised with a suitable starting point for our investigations – benzoic acid.

After reading the seminal work by Kim *et al*[42] on the generation of benzyne from *ortho*-substituted benzoic acid esters, we decided that benzoic acid could be a suitable starting point. Kim shows that benzyne can be produced from these compounds through a palladium catalysed process, culminating in the loss of carbon dioxide from an organopalladium intermediate.

In the proposed mechanism (shown in figure 3.1), the starting materials first underwent an oxidative addition of Pd(0) between the C–Br bond to generate the intermediates **139** and **142**. It is then hypothesised that the formation of the 5-membered-ring palladocycle **143** occurs *via* the loss of methyl bromide or potassium bromide. This key intermediate then decomposes with heat to regenerate the Pd(0)

species along with one molecule of benzyne. Lastly the benzyne then trimerises in the presence of Pd(0) to give the triphenylene **140** in moderate yields.[42]

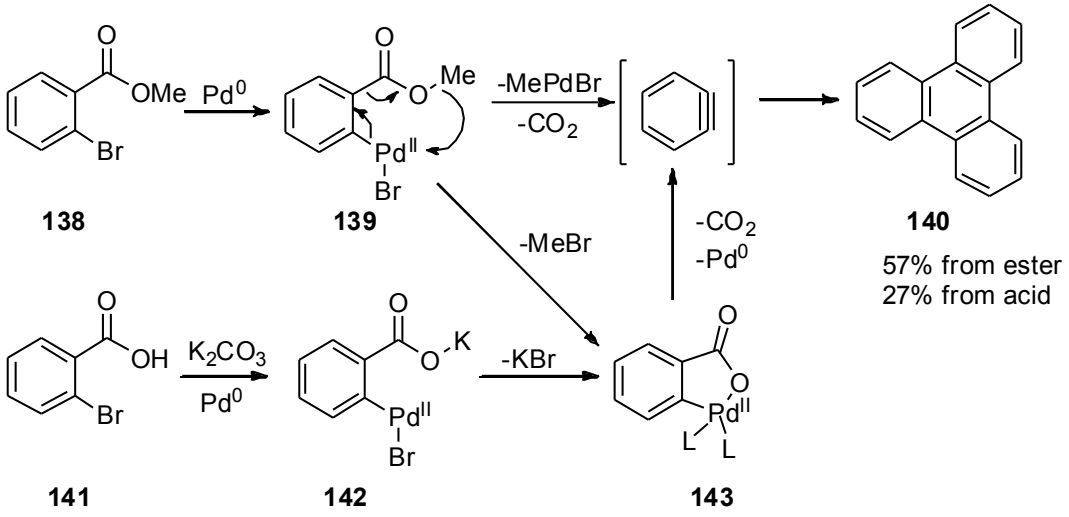


Fig. 3.1. The generation of benzyne from *ortho*-substituted benzoic acids and esters.[42]

It was the key intermediate **143** that first inspired us to generate benzyne from benzoic acid. This 5-membered palladocycle has recently been hypothesised as the intermediate in a variety of C–H activation protocols, and is accessed through the C–H activation of benzoic acid. There are numerous examples of utilising this palladocycle for a variety of C–C bond forming reactions and the field is still growing (figure 3.2.).[101-108]

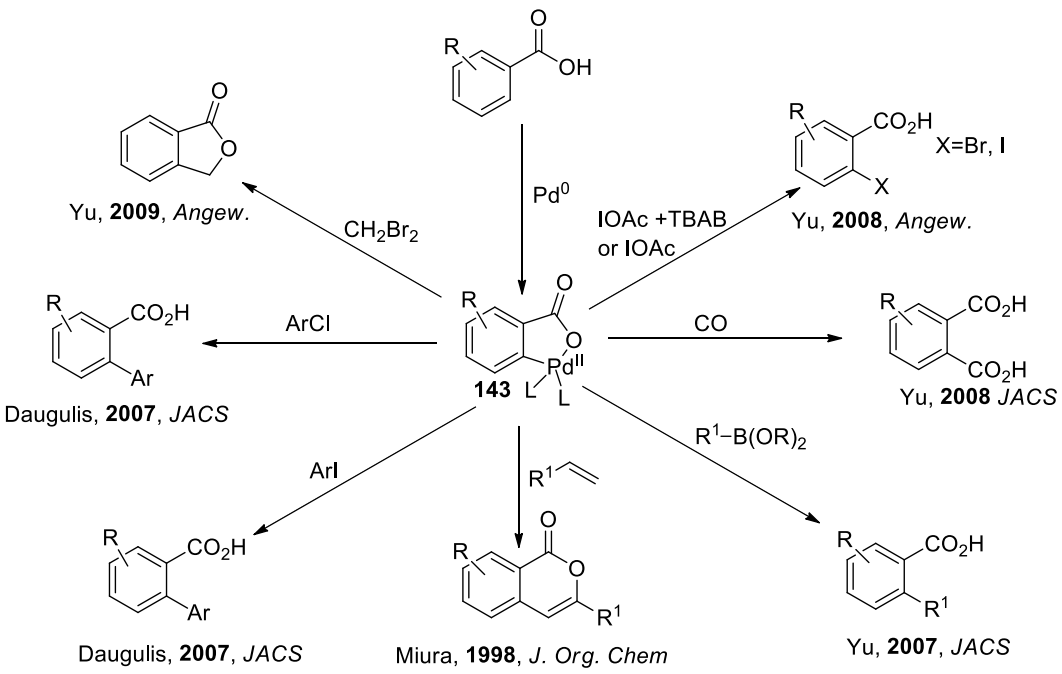


Fig. 3.2. The use of palladocycle **143** in organic chemistry.[101-107]

It was our aim to combine the methodology developed by Kim *et al* along with C–H activation in order to generate benzyne from benzoic acid. The details of the proposed reaction pathway are presented in figure 3.3. below.

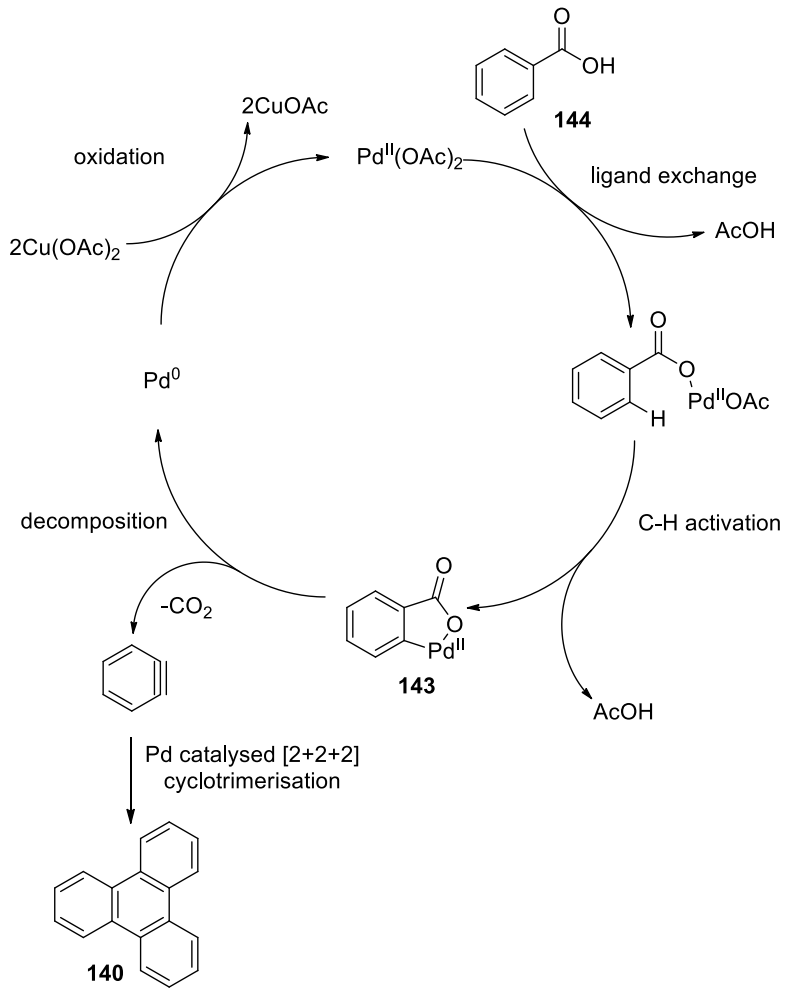


Fig. 3.3. The generation of benzyne from benzoic acid using C–H activation.

The reaction would begin with the formation of palladocycle **143** using the C–H activation technologies previously described. It is important to note that a Pd(II) source is required for the *ortho*-palladation of benzoic acid **144** in the first step. It is then hoped that in the absence of any external reactants the complex will break down with heat to release benzyne, carbon dioxide and Pd(0). It was decided to monitor the yield of benzyne formation by allowing its trimerisation to triphenylene **140**. The trimerisation of benzyne in the presence of Pd(0) is a very reliable reaction and there are numerous examples of its use in the literature.[32, 33, 109-115] As Pd(0) is released in the final step of the proposed sequence it is envisaged that an oxidant will be required in order to convert this species back to Pd(II).

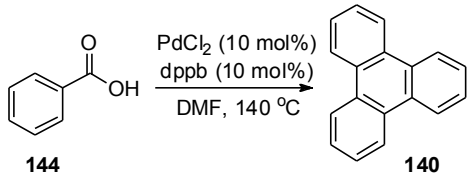
With a suitable hypothesis in hand we proceeded to investigate whether this reaction was possible in the laboratory.

3.1 Reaction Optimisation

We began our investigations using the unsubstituted benzoic acid **144** as starting material. Temperature, solvent, palladium source, oxidant and ligand were all varied and the reactions were monitored using TLC in the first instance, which enabled us to quickly determine whether triphenylene had formed.[1] After extensive searching, conditions were obtained that yielded <1% of triphenylene. It was at this point that we started to use GCMS to quantify our yields for the reaction. A calibration curve was constructed using the GCMS, using various triphenylene concentrations made from the compound bought from Sigma-Aldrich. This then allowed us to gather yields for our reactions using a minimal amount of manipulation (filtration through silica with ethyl acetate followed by an aqueous wash of the organic layer and finally making the solution up to 100 mL using a volumetric flask).

The original conditions developed involved using a palladium chloride/dppb catalyst system with DMF as the solvent at 140 °C. Building on this, a screen of various different additives including bases, acetate salts and the phase transfer catalyst TBAB was employed. All additives had been used previously to promote C–H activation technology in other systems. The results of this screen are detailed in table 3.1.1. below.

[1] See Appendix A for a full details of reagents used in reaction screens.

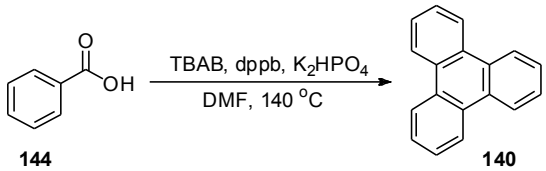


144 140

Entry	PTC	Additive	Yield (%)[a]
1	none	K_2HPO_4	0
2	none	KOAc	0
3	none	AgOAc	0
4	none	NaOAc	0
5	none	Cs_2CO_3	0
6	none	Na_2CO_3	0
7 [b]	TBAB	K_2HPO_4	5.6
8 [b]	TBAB	KOAc	0.5
9 [b]	TBAB	AgOAc	0
10 [b]	TBAB	NaOAc	0.8
11 [b]	TBAB	Cs_2CO_3	0.3
12 [b]	TBAB	Na_2CO_3	0

Table 3.1.1. A screen of chemical additives to the reaction. Reactions were heated to 140°C for 16 hours and were performed on a 0.09 mmol scale open to air using 0.5 mL of DMF and 10 mol% of catalyst and ligand. 2 equiv. of additive were added in each case. [a] GCMS yields. [b] 1 equiv. of TBAB was used.

The results from the screen were clear – there was definite advantage to be obtained in using both TBAB as a phase transfer catalyst and potassium phosphate dibasic as a base (Entry 7). With this in mind, further screens were performed, and in this instance oxidants were added in order to promote the recycling of the palladium catalyst (table 3.1.2.).



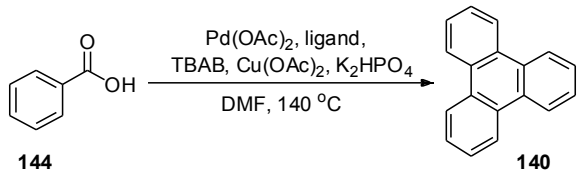
144 140

Entry	oxidant	Pd source	Yield (%)[a]
1	air	$PdCl_2$	0.4
2	Ag_2CO_3	$PdCl_2$	0
3	benzoquinone	$PdCl_2$	0
4	$Cu(OAc)_2$	$PdCl_2$	1.1
5	AgOAc	$PdCl_2$	0
6	$CuCl_2$	$PdCl_2$	0
7	CuO_2	$PdCl_2$	0
8	AgO_2	$PdCl_2$	0
9	$PhI(OAc)_2$	$PdCl_2$	0
10	air	$Pd(OAc)_2$	0
11	Ag_2CO_3	$Pd(OAc)_2$	0
12	benzoquinone	$Pd(OAc)_2$	0
13	$Cu(OAc)_2$	$Pd(OAc)_2$	4
14	AgOAc	$Pd(OAc)_2$	0
15	$CuCl_2$	$Pd(OAc)_2$	0
16	CuO	$Pd(OAc)_2$	0
17	Ag_2O	$Pd(OAc)_2$	0
18	$PhI(OAc)_2$	$Pd(OAc)_2$	0

Table 3.1.2. A screen of oxidants. Reactions were heated to 140°C for 16 hours and were performed on a 0.09 mmol scale using 0.5 mL of DMF and 10 mol% of catalyst and ligand in a sealed tube (with the exception of entries 1 & 10), 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 1 equiv. of oxidant were added in each instance. [a] GCMS yields.

The data in table 3.1.2 shows a selection of results from a much larger screen which also involved ligand screening. In all instances copper(II) acetate was found to be the only oxidant which promoted the reaction successfully (entries 4 & 13). In addition to this, palladium(II) acetate was found to be a better palladium source than palladium(II) chloride in the reaction. Further investigation was employed on these reactions and it was found that reactions performed in sealed tubes, or under a

nitrogen or oxygen atmosphere did not perform as well as those open to air. With this in mind, a ligand screen was then set up with a selection of 9 ligands (table 3.1.3.). All reactions were conducted open to air in accordance with what we had just discovered.



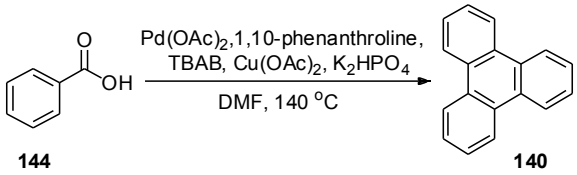
144 140

Entry	ligand	Yield (%)[a]
1	dppb	4.0
2	diphenylphosphinopentane	3.7
3	xanthene	4.0
4	2,2'-Bipyridyl	4.5
5	6,6'-dibromo-1,1'-bi-2-napthol	2.7
6	1,3,5-triazaphosphaadamantane	2.2
7	(R)-(+)-1,1'binapthyl-2,2'-diamine	4.4
8	1,10-phenanthroline	6.9[b]
9	(2-biphenyl)di-*tert*-butylphosphine	7.4

Table 3.1.3. A screen of ligands. Reactions were performed on a 0.09 mmol scale using 0.5 mL of DMF open to air. 10 mol% $Pd(OAc)_2$, 10 mol% ligand, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 1 equiv. of $Cu(OAc_2)$ were added and the reaction was heated to 140 °C O/N. [a] GCMS yields. [b]This reaction was found to be much cleaner than any of the others in the series.

The ligand screen showed that a variety of ligands were viable in the reaction. The two compounds that stood out however, were the Buchwald ligand (2-biphenyl)di-*tert*-butylphosphine and the heterocyclic ligand 1,10-phenanthroline. Both ligands enabled yields in the region of 7% to be acheived– almost twice that which we had previously achieved. It was decided to take forward the 1,10-phenanthroline ligand for further testing as the reaction utilising this ligand was found to be much cleaner than any of the others tested. At this stage, the Buchwald ligand was set-aside for further investigation at a later stage.

The next parameter to be examined was the reaction concentration. Varying amounts of DMF solvent were added to determine its effect on the reaction (Table 3.1.4.).

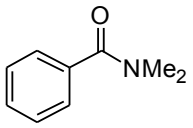


144 140

Entry	Amount of DMF in reaction (mL)	Yield (%)[a]
1	0.5	3.9
2	1	7.4
3	1.5	10.8
4	2	9
5	2.5	8.1
6	3	6.9

Table 3.1.4. A screen of reaction concentration. Reactions were performed on a 0.09 mmol scale using DMF as solvent, open to air. 10 mol% $Pd(OAc)_2$, 10 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 1 equiv. of $Cu(OAc_2)$ were added and the reaction was heated to 140 °C O/N. [a] GCMS yields.

It was found that solvent concentration had a profound effect on the yields of the reaction. By adding just 1 mL extra of solvent to the reaction we could more than double the yield over the standard conditions in this series. It was found that when more than 1.5 mL of solvent was used, the decomposition products from the DMF started to interfere with the reaction. DMF decomposes releasing dimethylamine at high temperatures and the presence of a peak with mass 149 in our GCMS trace led us to hypothesise that the amide by-product **145** might be formed under these more dilute conditions.



145a

Fig. 3.1.1. The formation of amide by-product **145a**.

It was also noted at this point, that a second by-product **145b** was formed in the reaction. The formation of this by-product presumably arises from a benzyne insertion into palladocycle **143** as illustrated in figure 3.1.2.

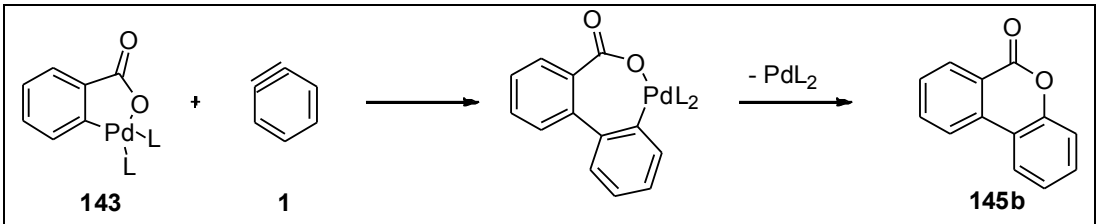
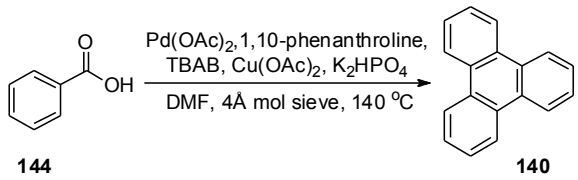


Fig. 3.1.2. The formation of chromanone by-product **145b**.

The next parameters to be investigated were the choice of solvent and the number of equivalents of copper acetate (table 3.1.5.). Initial solvent screens showed that the reaction tended to work better with high boiling polar solvents. The reaction worked with varying degrees of success with NMP, DMA and diglyme, but it was DMF and sulfolane that were found to be the most favourable solvents for the reaction. In order to maintain dry reaction conditions molecular sieves were added to the mixture and were found to benefit the reaction.



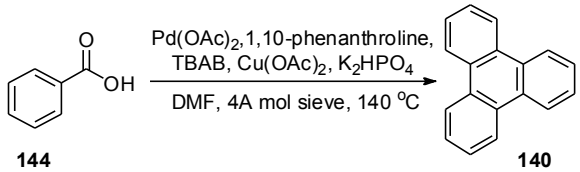
Entry	solvent	Copper (II) Acetate equivalents	Yield (%)[a]
1	DMF	0.5	10
2	DMF	0.75	28
3	DMF	1	18
4	DMF	2	0
5	sulfolane	0.5	17
6	sulfolane	0.75	26
7	sulfolane	1	12
8	sulfolane	2	0

Table 3.1.5. A screen of equivalents of copper acetate. Reactions were performed on a 0.09 mmol scale using 1.5 mL of solvent open to air. 10 mol% $Pd(OAc)_2$, 10 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4 and 1 equiv. of TBAB were added and the reaction was heated to 140 °C O/N. [a] GCMS yields.

It was found that the number of equivalents of copper(II) acetate used in the reaction was critical in obtaining a good yield. It was observed that excess equivalents of

copper(II) acetate led to exclusive formation of the chromanone by-product **145b**. In addition to this, too little copper(II) acetate lead to poor catalyst turnover and hence lower yields. A suitable compromise was to use 0.75 equivalents of the oxidant in the reaction. When this amount was used, none of the chromanone by-product was observed and we had suitable catalyst turnover to give us a 28% yield of product.

At this point the temperature of the reaction was revisited (table 3.1.6.). Initial results had shown that high temperatures of 140 °C were required to start the reaction. However, optimum temperature conditions had not yet been determined.



144 140

Entry	Solvent	Temperature (°C)	Yield (%)[a]
1	DMF	120	5
2	DMF	130	15
3	DMF	140	19
4	Sulfolane	120	11
5	Sulfolane	130	30
6	Sulfolane	140	37
7	Sulfolane	150	37

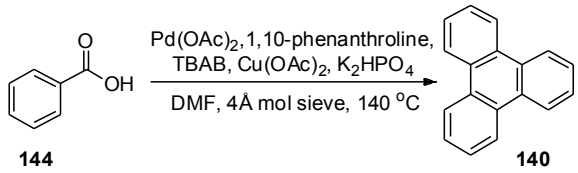
Table 3.1.6. A screen of temperature. Reactions were performed on a 0.09 mmol scale using 1.5 mL of solvent open to air. 10 mol% $Pd(OAc)_2$, 10 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated O/N. [a] GCMS yields.

The reaction screen found that 140 °C was the optimum temperature for the reaction and that sulfolane had a definite advantage over DMF. Interestingly however, we had managed to achieve a 37% yield for the reaction (an increase in yield of 9%) without actually changing the reaction conditions. With this surprising outcome, the physical construction of the experiment was scrutinised. Two possible sources of error were hypothesised to account for the experimental discrepancy – the temperature of the heating blocks and the preparation of the samples.

The temperature of the heating blocks was considered a concern as they took a long time heat up. In this temperature screen, efforts were made to ensure that the heating blocks were at the correct temperature at the start of the reaction and this could have resulted in the higher yields. In other screens, the reaction vessel was placed in the block whilst it was still trying to achieve its starting temperature. This would have allowed the reactions to react at lower temperatures than those desired, before finally reaching the required temperature. It was decided to ensure that all heating blocks were at temperature before the reaction vessels were added.

Next, the use of stock solutions was examined. Whenever possible, stock solutions of solvent, benzoic acid, catalyst and ligand were used in order to minimise the amount of weighing required to set up the reactions. This saved time, but also increased the accuracy of the weighing – it is easier to weigh out 20 mg of catalyst accurately for 10 reactions, than to weigh out 2 mg for one. In order to homogenise the stock for the reaction, the mixture had to be sonicated for around 1 minute. As this process was only performed when stock solutions were used, then this might be a source of discrepancy.

In order to investigate this, a small reaction screen was set up examining the effect of sonication on the reaction – did it just help to solubilise the reagents or did it itself actually promote the reaction (Table 3.1.7.)? It was soon found that the use of sonication to solubilise the reaction was definitely beneficial. When the reaction was performed using the optimum conditions we had at that time (table 3.1.6, entry 6), but without sonication, a yield of only 13% was obtained (Entry 1). When the solvent, benzoic acid, catalyst and ligand were sonicated prior to the reaction, a much higher yield of 25% was obtained. Reactions with only sonication and no heating yielded no product, discounting the possibility that sonication itself promotes the reaction. As a consequence of these results, all reactions were sonicated prior to heating, regardless of whether stock solutions were employed.

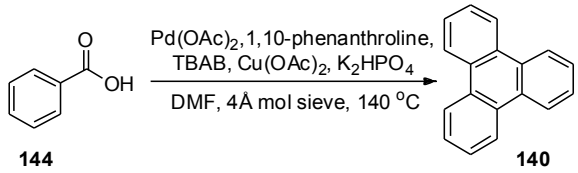


144 140

Entry	Conditions	Yield (%)[a]
1	No sonication prior to heating at 140 °C O/N	13
2	Sonication of reaction prior to heating at 140 °C O/N	25
3	Only sonication	0

Table 3.1.7. The effect of sonication. Reactions were performed on a 0.09 mmol scale using sulfolane as solvent open to air. 10 mol% $Pd(OAc)_2$, 10 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added. [a] GCMS yields.

With the source of the discrepancy identified we continued our screening. It was decided that a concentration screen should be conducted as we were using a new solvent. The results of which are detailed in table 3.1.8.



144 140

Entry	Amount of Sulfolane in Reaction (mL)	Yield (%)[a]
1	0.5	12
2	1	31
3	1.5	26
4	2	39
5	2.5	47
6	3	42

Table 3.1.8. A screen of reaction concentration. Reactions were performed on a 0.09 mmol scale using sulfolane as solvent open to air. 10 mol% $Pd(OAc)_2$, 10 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated to 150 °C O/N. [a] GCMS yields.

It was found that the reactions using sulfolane solvent could be performed at higher dilutions than those in DMF. Sulfolane does not decompose at higher temperatures in the same way that DMF does, and therefore, more can be used without the problem of

decomposition products interfering with the reaction. It was found that using 2.5 mL of sulfolane was the optimum dilution for the reaction, giving an acceptable yield of 47%. This was a considerable increase from the <1% yield achieved which we started the GCMS screening with and we were pleased with this result.

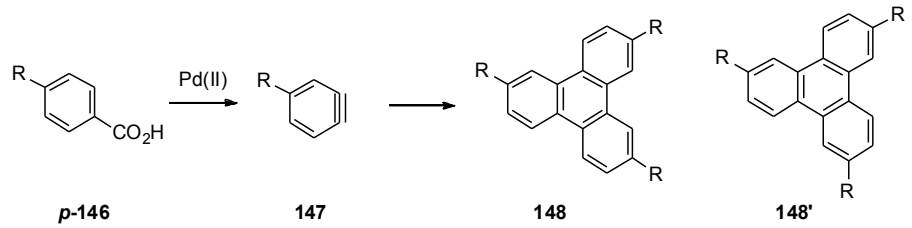
Further screening was attempted on the reaction to try and achieve greater yields but all attempts were found to be unsatisfactory. Microwave reactions, reactions using syringe pump addition of the benzoic acid, screens of phase transfer catalysts, screens of potassium phosphate dibasic and TBAB stoichiometries and extensive ligand screens (~40 different ligands) were all performed in the hope of increasing the yield, but all were to no avail.[2] There was precedent for the generation of other 5-membered metallocycles from benzoic acid in the literature,[116-118] so various different nickel, platinum, rhodium, rhenium, iridium and copper catalysts were also employed in the reaction. Unfortunately, none of these catalysts were found to be successful.

All in all, almost 750 iterations of the reaction were conducted to eventually provide us with the optimum conditions detailed in entry 5, table 3.1.8. The next task was to scale the reaction up and to achieve an isolated yield. It was found that in order to obtain similar yields on scale up, the slightly higher catalsyt loading of 12.5 mol% was required along with the higher temperature of 150 °C.

[2] See Appendix A for full details of raegents and conditions used in reaction screens.

3.2 Exploring the Scope of Benzoic Acids

We applied our developed conditions to a variety of different benzoic acids to assess the scope of the reaction. The results of which are detailed in table 3.2.1.



p-**146** **147** **148** **148'**

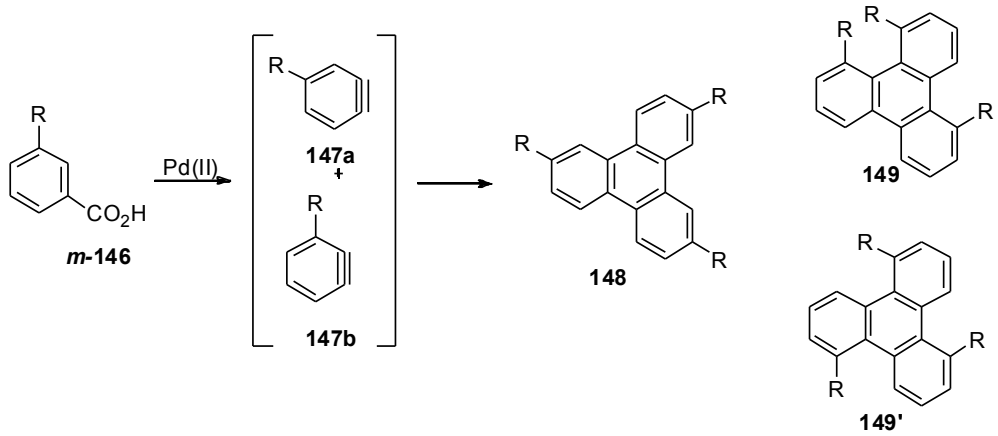
Entry	Product	R	Yield (%)[a]
1	**148a**	Me	34
2	**148b**	t-Bu	33
3	**148c**	OMe	18
4	**148d**	F	35
5	**148e**	NO_2	0
6	**148f**	Br	0
7	**148g**	CO_2Me	0
8	**148h**	Ac	0
9	**148i**	NMe_2	0
10	**148j**	CN	0

Table 3.2.1. Exploring the scope of *para*-substituted benzoic acids. Reactions were performed on a 0.9 mmol scale using 25 mL of sulfolane as solvent open to air. 12.5 mol% $Pd(OAc)_2$, 12.5 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated to 150 °C O/N. [a] Isolated yields.

The scope of the reaction with respect to benzoic acids was found to be somewhat disappointing – nitro, bromo, ester, acetyl, amine and nitrile groups were all found not be viable in the reaction, even when tried at the alternative temperatures of 140 °C and 160 °C. A few simple examples did work however, and gave some interesting results. When the reactive aryne intermediates **147** are formed, there are two possible ways in which they can trimerise. They can trimerise C_3 symmetrically to give

product **148'** or give unsymmetric products of the type **148**. In all instances, only the unsymmetrical regioisomer **148** was formed. This observation is concurrent with other trimerisations of aryne intermediates from more conventional benzyne precursors and is good evidence of the aryne intermediacy.[32, 42] It was found that the simple alkyl groups methyl and *tert*-butyl worked well with moderate yields of 34% and 33% respectively. In addition to this, the fluoro and methoxy derivatives also worked giving 35% and 18% yields of the triphenylene products.

We next examined *meta*-substituted benzoic acids, the results of which are detailed in table 3.2.2. below.

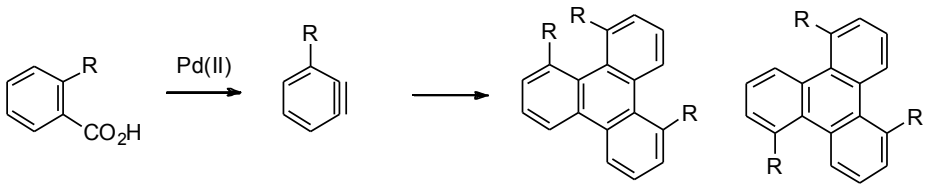


Entry	R	Product	Yield (%)[a]
1	Me	**148a**	35
2	CF_3	**148k**	19[b]
3	F	**148d**	12
4	NO_2	**148e**	0
5	NMe_2	**148i**	0
6	OMe	**148c**	0

Table 3.2.2. Exploring the scope of *meta*-substituted benzoic acids. Reactions were performed on a 0.9 mmol scale using 25 mL of sulfolane as solvent open to air. 12.5 mol% $Pd(OAc)_2$, 12.5 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated to 150 °C O/N. [a] Isolated yields. [b] Reaction was performed at 160 °C.

With the *meta*-substituted benzoic acid there is the possibility of benzyne forming in two places on the aromatic ring. When the experiments were performed on the methyl and fluoro derivatives, it was found that the same products as those from the *para*-substituted derivatives were formed. This indicated that the same aryne intermediate **147a** was forming in the process. None of the other possible regioisomeric products **149** and **149'** were isolated from the reaction mixture, which indicates that aryne intermediate **147b** was not formed in the reaction. Again, the results were not very encouraging, giving poor yields and small substrate scope.

To complete our investigations into the mono-substituted derivatives, *ortho*-substituted benzoic acids were examined (Table 3.2.3).



***o*-146** **147b** **149** **149'**

Entry	R	Product	Yield (%)[a]
1	Me	**149a**	23
2	OMe	**149b**	0
3	F	**149c**	0

Table 3.2.3. Exploring the scope of *ortho*-substituted benzoic acids. Reactions were performed on a 0.9 mmol scale using 25 mL of sulfolane as solvent open to air. 12.5 mol% $Pd(OAc)_2$, 12.5 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated to 150 °C O/N. [a] Isolated yields.

As with the *meta* and *para*-derivatives, complete regioselectivity was observed in favour of the unsymmetric regioisomer. Complete selectivity for regioisomer **149** was observed in the reaction with none of the C_3 symmetric regioisomer **149'** isolated. The *ortho*-substituted derivatives were generally ineffective in the reaction, with only the *ortho*-toluic acid derivative **146a** providing a poor yield of only 23%.

Lastly the pyridine derivatives of benzoic acids and disubstituted benzoic acids were examined as illustrated in figure 3.2.1. Disappointingly, all of these derivatives were found not to be viable in the reaction.

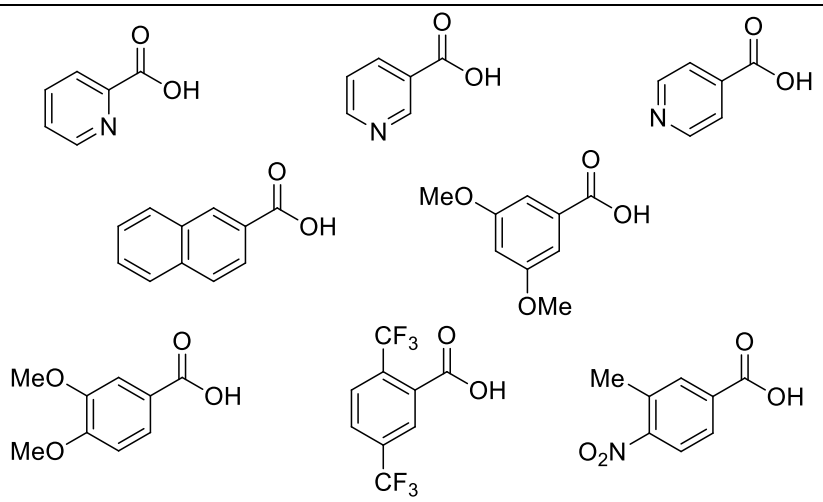
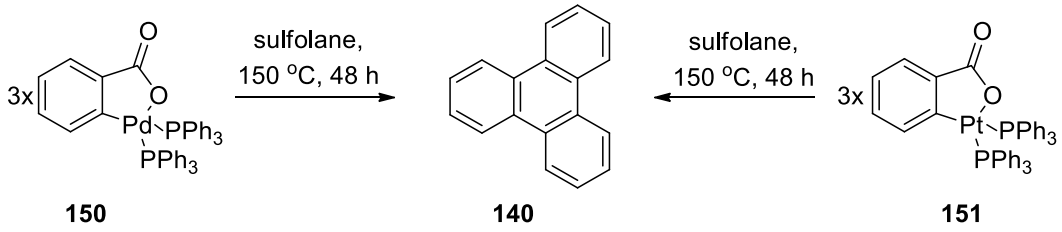


Fig. 3.2.1. Many substituted benzoic acids which were not viable for the generation of arynes.

3.3 Exploring the Mechanism of Benzyne Formation from Benzoic Acid

In order to gain insight into the reaction mechanism for the production of benzyne from benzoic acid, it was hoped that some stoichiometric decomposition studies of metallocycles could be conducted. Metallocycles **150** and **151** which are similar to that of palladocycle **143** were synthesised. These palladocycles were then subjected to conditions similar to those described for the production of benzyne. It was hoped that we would observe the formation of benzyne from the decomposition of the products in the form of the trimerised product triphenylene. Unfortunately, even after extended heating times, no triphenylene or any other benzyne derived products were observed.



150 **140** **151**

Fig 3.3.1. The decomposition of metallocycles to benzyne to form triphenylene **140**.

It is thought that this may be due to the trimerisation of benzyne being hindered by stoichiometric amounts of the palladium catalyst. When the reaction was performed under standard conditions, but with a stoichiometric amount of catalyst, similar results were observed where no triphenylene was formed.

Further invesigations into the mechanism for the reaction will involve computational studies on the reaction. This work will be carried out by another member of the group.

3.4 Reacting Benzyne Derived From Benzoic Acid

It was decided to move on from exploring the substrate scope of the aryne generation and subsequent trimerisation to triphenylenes. The yields observed were not practicable and a new direction had to be taken with this chemistry. Examining the reaction system, it was decided that the making of triphenylenes might not be the best way to quantify yields on this reaction. In order to produce triphenylenes, 3 molecules of benzyne are required to form at any one time, forcing us to quicken reaction times by increasing the temperature. It was decided that perhaps higher yields could be obtained at lower temperatures if trapping experiments were conducted. This would require the formation of only one molecule of benzyne at any one time and thus would negate the higher temperatures required.

A variety of known aryne reactions were considered and substrates were chosen to react with benzyne generated under the new reaction conditions.

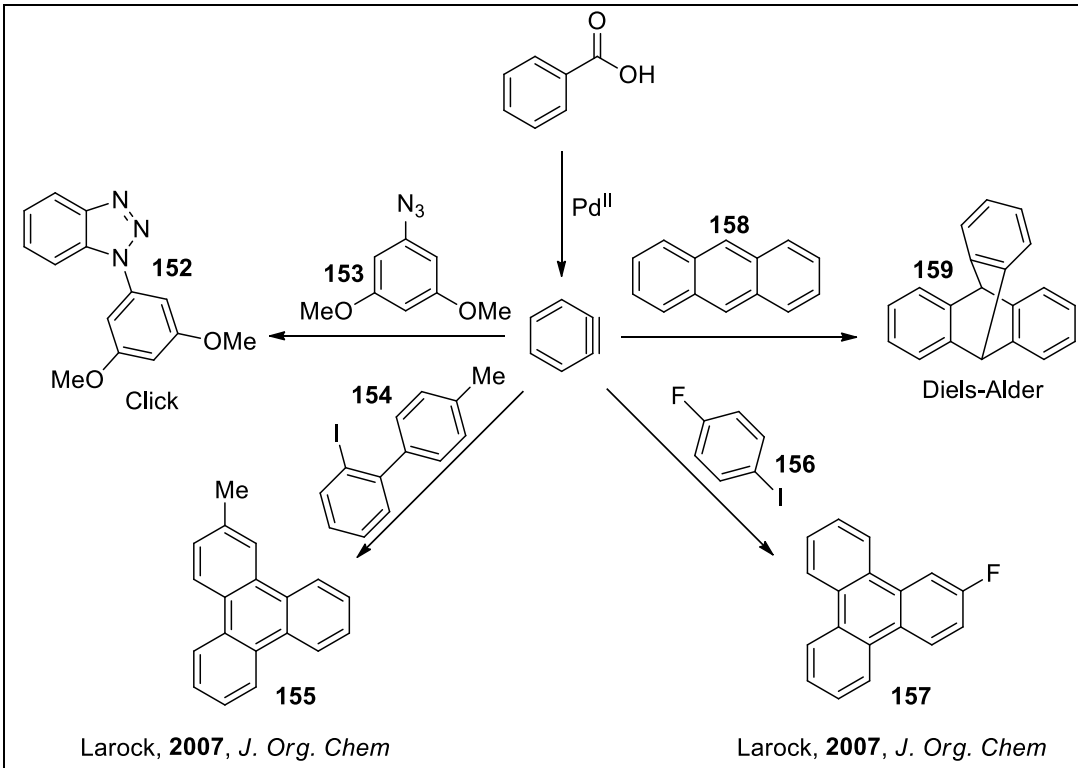


Fig. 3.4.1. The reactions attempted with benzyne generated from benzoic acid.[62]

In the first instance, the fundamental aryne chemistry reaction – the Diels-Alder reaction with benzyne, was tried. We were somewhat confident that this reaction would work and were rather surprised when the anthracene **158** did not participate in the reaction. Unreacted anthracene and triphenylene were the only two compounds isolated from the reaction.

We next turned our attention to the click reaction, another well documented reaction in aryne chemistry.[15, 21, 22, 119, 120] In this case, it was found that not only did the reaction not provide any of the benzotriazole product **152** desired, but the starting material **153** completely impeded the reaction. No triphenylene was formed in this reaction, indicating that the presence of the azide interfered with benzyne formation.

Although the source of failure for the click reaction could be attributed to the incompatibility of azides with our reaction, the cause of the failure of the Diels-Alder reaction was not obvious. One possible hypothesis is that the palladium bound benzyne is not viable in the reaction. It was therefore decided to attempt chemistry which had already been shown to involve a pallado-benzyne species. Larock and co-workers published a paper on the highly efficient route to fused polycyclic aromatics *via* palladium-catalysed aryne annulation by aryl halides. In this article, he describes the palladium catalysed reaction of halobiaryls **154** and aryl halides **156** with benzyne to generate triphenylenes **155** and **157** in good yields (see figure 3.4.1.).[62]

It was found that for these reactions, none of the desired products were obtained. For the reaction with aryl halide **156**, no benzyne derived products were observed, indicating that the reactions were not compatible. For the halobiaryl **154**, triphenylene formation was observed, but without the appended methyl group. This indicated that the halobiaryl **154** did not participate in the reaction.

The lack of success with these reactions was discouraging and it was decided to approach the reaction from a different angle. It was decided that intramolecular aryne reactions would be more facile and might give us some useful applications for the chemistry. The reactions tried are detailed in figure 3.4.2. below.

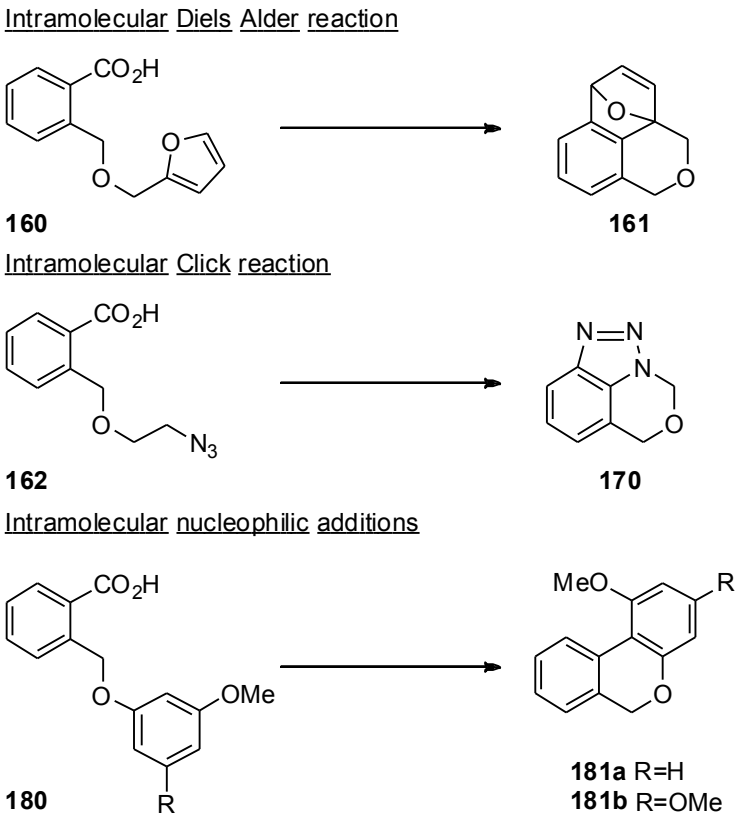


Fig. 3.4.2. The intramolecular aryne reactions attempted.

Three intramolecular reactions were decided upon. The Diels-Alder reaction[121, 122] and the nucleophilic addition of an electron rich aromatic ring to benzyne[123] were already known in the literature, and it was also decided to try an intramolecular click reaction. In all instances no reaction was observed. All starting materials remained unchanged and no trace of the intramolecular cyclisation products were observed. It was thought that this could be due to the difficulty of generating benzyne from *ortho*-substituted benzoic acids as observed earlier.

It was finally decided that the best course of action was to find a reaction which was as analogous to the trimerisation of benzyne as possible. The [2+2+2] cycloaddition of a ground state alkyne with benzyne to generate phenanthrenes **182** and naphthalenes **183** seemed like a close enough match (see figure 3.4.5.). This work had been published previously by two different groups using the silyl aryl triflates as benzyne precursors. The work was shown to have good yields and so was an ideal reaction system for our investigations.[29, 34, 35]

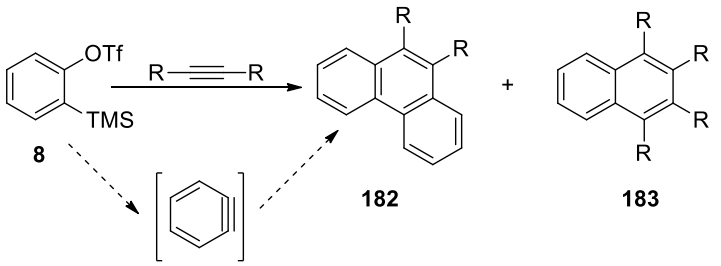
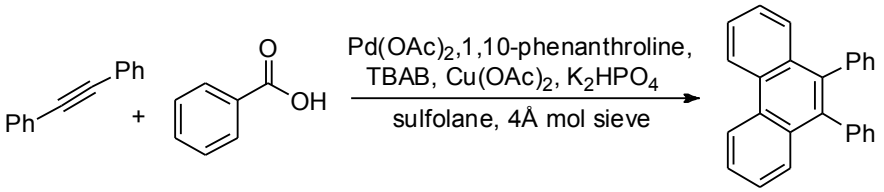


Fig. 3.4.5. The trimerisation of benzyne with alkynes to generate phenanthrenes and naphthalenes.[29, 34, 35]

By altering the stoichiometries of the reagents in these reactions the formation of either the phenanthrene **182** or naphthalene **183** product can be favoured. We began our investigations by focussing on generation of the phenanthrene product **185**. Initial reactions used the standard conditions developed previously for benzyne formation from benzoic acid, in combination with the addition of the alkyne diphenylacetylene **184** to the reaction mixture. To our delight a 26% yield of the phenanthrene product was obtained when the reaction was first tried with 1 equivalent of diphenylacetylene added to the reaction mixture. With this encouraging result, the reaction was optimised and the results are detailed in table 3.3.1. below.



184 **185**

Entry	No. of equivalents of alkyne	Temperature (°C)	Yield (%)[a]
1	0.33	150	15
2	0.67	150	17(22)[b]
3	1	150	12(24)[b]
4	1.5	150	8(26)[b]
5	0.125	140	45
6	0.125	130	48
7	0.125	120	16

Table 3.4.1. Preparation of phenanthrene **185** from the reaction of benzyne derived from benzoic acid and diphenylacetylene **184**. Reactions were performed on a 0.9 mmol scale using 25 mL of sulfolane as solvent open to air. 12.5 mol% $Pd(OAc)_2$, 12.5 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated O/N. [a] Isolated yields. [b] Numbers in brackets are yields based on benzoic acid when it was the limiting reagent.

Initial reactions were used to determine yields based on the amount of benzoic acid used in the reaction (and therefore the amount of benzyne formed) and it was found that when 1.5 equivalents of the alkyne was used we could achieve a 26% yield of phenanthrene. This reaction was found to be rather messy and the naphthalene by-product **186** and a fluorene by-product **190** were also isolated in 23% and 18% yields respectively.

The mechanism for the formation of fluorene **190** is not immediately clear but a possible pathway is described in figure 3.4.6. below. The reaction starts in a similar fashion to the [2+2+2] mechanisms followed for the production of phenanthrene and naphthalene products, and palladocycle **187** is formed. A heterolytic cleavage of the Pd–C bond then produces the olefinic intermediate **188**. This intermediate then undergoes C–H activation to produce the palladocycle **189** which reductively eliminates to give fluorene **190**.

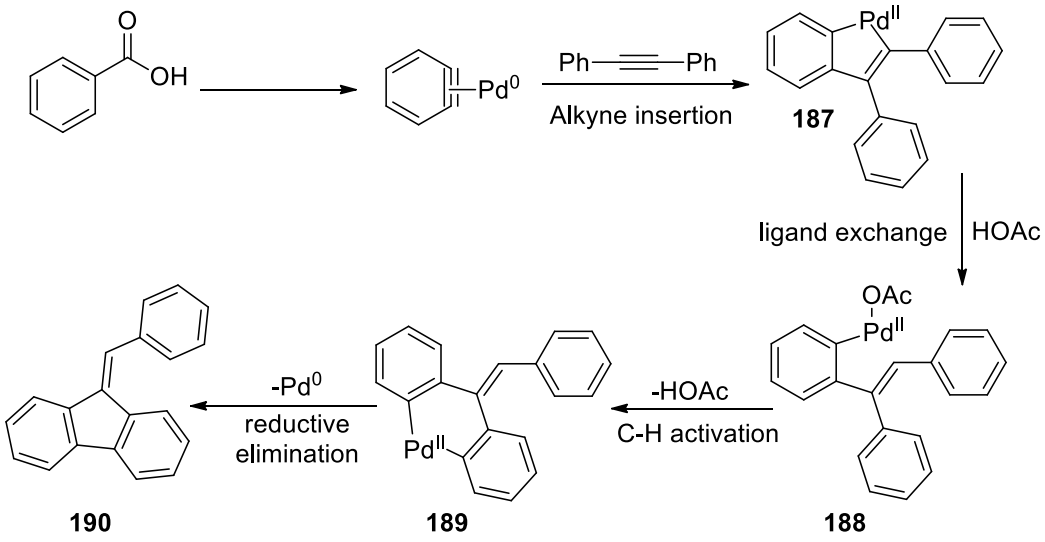
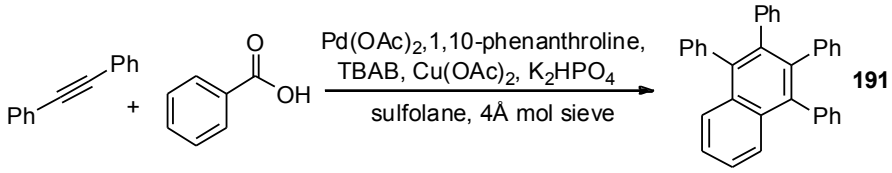


Fig. 3.4.6. Postulated mechanism for the formation of the fluorene **190**.

Due to the formation of these side-products the calculation of yields based on aryne formation was deemed to be an unsuccessful strategy. In order to produce the phenanthrene, 2 molecules of benzyne and 1 molecule of alkyne is required. It therefore makes more sense to have an excess of benzoic acid and calculate the yields based on the alkyne.

The second set of results follow this strategy and using an excess of 8 equivalents of benzoic acid, a temperature screen was set up (Table 3.3.1, entries 5-7). The excess of alkyne soon addressed the problem of the formation of by-products and the yields reflect a cleaner reaction. It was found that the optimum temperature for the reaction was the slightly cooler temperature of 130 °C, and under these conditions a 48% yield of phenanthrene **185** could be obtained (Entry 6).

This was the highest yield that we could achieve for this reaction and so we turned our attention to production of the naphthalene derivative **191**. To produce the naphthalenes, 1 equivalent of benzyne and 2 equivalents of alkyne are required. Therefore an excess of alkyne was used in the reaction and the yields were calculated based on benzoic acid.



Entry	No. of equivalents of alkyne	Temperature (°C)	Yield (%)[a]
1	1.5	150	29
2	3	150	42
3	6	150	50
4	6	135	55
5	6	120	69
6	6	110	45

Table 3.4.2. Preparation of naphthalene **191** from the reaction of benzyne derived from benzoic acid and diphenylacetylene. Reactions were performed on a 0.9 mmol scale using 25 mL of sulfolane as solvent open to air. 12.5 mol% $Pd(OAc)_2$, 12.5 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 0.75 equiv. of $Cu(OAc)_2$ were added and the reaction was heated O/N. [a] Isolated yields.

When forming the naphthalenes, temperature was found to be the key parameter in the reaction. It was found that the reaction could be performed at the much lower temperature of 120 °C and gave the much higher yield of 69% of product. In the initial screens of the project, high temperatures were required for triphenylene formation as 3 molecules of benzyne had to be generated at a time. As this is not the case for naphthalene formation, the lower temperature of 120 °C can be used, resulting in a much cleaner, more efficient and higher yielding reaction.

It must be said however, that there is postulation in the literature that the naphthalene products may indeed be formed through a non-benzyne mechanism. Miura and co-workers[117] published a paper on the rhodium and iridium-catalyzed oxidative coupling of benzoic acids with alkynes *via* regioselective C−H bond cleavage. In this paper, they describe the treatment of benzoic acid with alkynes and iridium catalysis to generate naphthalene products. They hypothesise that the mechanism goes *via* a stepwise C–H activation, alkyne insertion, decarboxylation and finally another alkyne insertion (see figure 3.4.7). They also explain the formation of the two regioisomers **192** and **193** through a protonation and cycloiridation cycle which is probably driven

through steric interactions. Although the transition metal used is different, this chemistry is analogous to that which we had just conducted. As there was no immediate way to determine which mechanism was proceeding in the reaction; it was decided that the naphthalene formation should not be the main focus of this work, even though it gave higher yields.

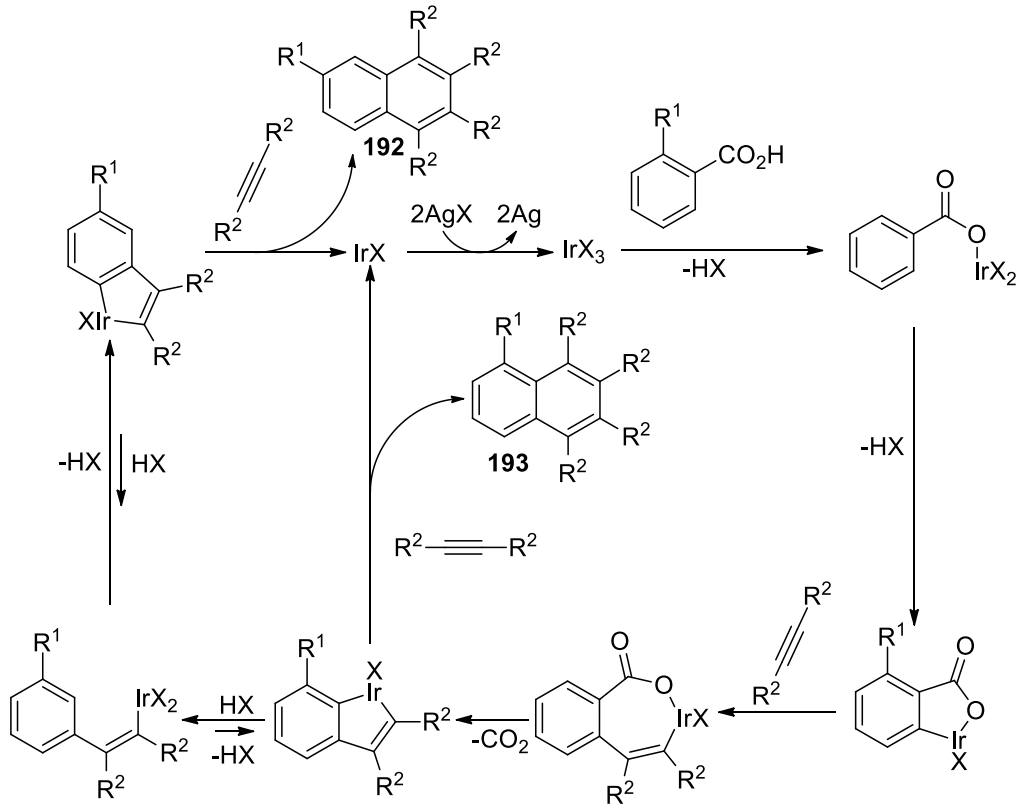
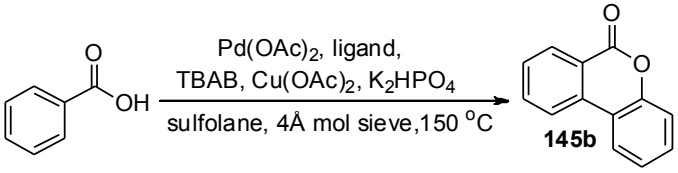


Fig. 3.4.7. Postulated mechanism for the iridium catalysed reaction of benzoic acid and alkynes to generate naphthalene.[117]

The last reaction that was investigated in this reaction series was the formation of the chromanone by-product **145b** (Table 3.3.3.). The formation of the by-product was decided to be a sufficiently interesting reaction to warrant some further investigation. It was found that the reaction could be made to go in 25% yield by increasing the amount of copper(II) acetate to 2 equivalents and using *tert*-butyl XPhos as ligand (Entry 3).



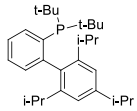
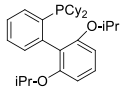
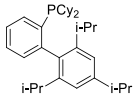
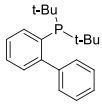
Entry	ligand	yield (%)[a]
1	Tricyclohexylphosphine	18
2	Tris(4-methoxyphenyl)phosphine	22
3		25
4		8
5		0
6		10
7	1,10-phenanthroline	trace

Table 3.4.3. Making chromanone **145b** from the reaction of benzyne derived from benzoic acid. Reactions were performed on a 0.9 mmol scale using 25 mL of sulfolane as solvent open to air. 12.5 mol% $Pd(OAc)_2$, 12.5 mol% 1,10-phenanthroline, 2 equiv. of K_2HPO_4, 1 equiv. of TBAB and 2 equiv. of $Cu(OAc)_2$ were added and the reaction was heated to 150 °C O/N. [a] Isolated yields.

The production of the chromanone **145b** could not be made to go in more than 25% yield and therefore no additional work was performed on this reaction. The project was deemed complete and the results were compiled for publication and accepted in the journal Chemical Communications.[124]

3.5 Conclusions

In conclusion, a novel method of generating benzyne from cheap and readily available benzoic acids has been developed. This methodology was used in the first instance to make triphenylenes from the trimerisation of benzyne. The yields were found to be moderate for simple benzoic acids and showed poor substrate scope giving either low yields or no product when substituted benzoic acids were employed.

A range of aryne reactions were then tried with the new method of benzyne generation. It was found however, that most were not compatible with the methodology. One example which did work well with the methodology was the trimerisation of alkynes with benzyne. This process yielded moderate quantities of phenanthrene products, but more importantly afforded good yields of naphthalenes indicating that a high yield of benzyne could be produced. However, the presence of a possible alternate mechanism for the formation of naphthalene products prevented this from becoming the main focus of the work.

It was also found that the methodology could be altered slightly to produce the benzo-fused lactone **145b**, albeit in low yields. These products originated from the interaction of benzyne with the palladocycle **143**.

At this point the results were compiled for publication and were accepted in the journal Chemical Communications. Initial studies to prove the reaction mechanism on this project were found to be inconclusive.[3] Therefore, future work on this project will consist of computational calculations in the hope of gaining further insight into the reaction and its mechanism.

[3] See Appendix B.

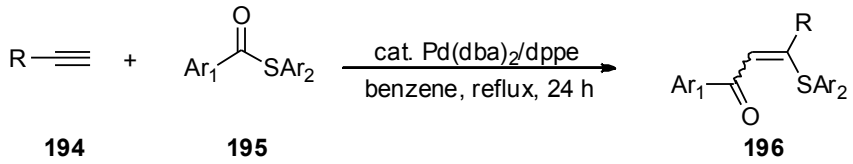
4 The Insertion of Benzyne into Thioesters

The introduction of *o*-triflatosilanes as benzyne precursors has resulted in a renaissance of aryne chemistry. The fact that these reactions can now be performed cleanly, in high yields and under mild conditions compatible with transition metal catalysed chemistry, has allowed a 'user friendly' approach to aryne chemistry. As a result, this chemistry is now practiced across the world and is an incredibly attractive and current field to be working in.

There are a number of areas in which benzyne chemistry is now considered to be an efficient tool for the organic chemist. The traditional aryne reactions such as nucleophilic additions to arynes and pericyclic reactions with benzyne have been revisited and have shown remarkable improvements using the new chemistry. In addition to this, new areas of aryne chemistry have also evolved – the insertion of benzyne into sigma bonds and palladium catalysed reactions are two of the more popular areas.

Previous work in the group had consisted of aryne sigma-bond insertion into the C–N bond of amides and the success achieved in this research led us to investigate possible expansions of this methodology.[125] The insertion of arynes into thioesters and esters was as yet unknown, and the possibilities of building on previous success in this field led us to investigate these reactions.

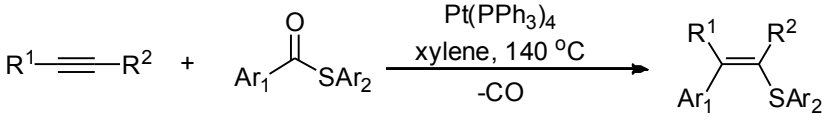
Upon research of the literature, an analogous reaction for benzyne insertion into thioesters was found. Similar chemistry had been performed previously with alkynes by Kambe and co-workers[126] and provided valuable insight into insertion reactions into thioesters. In the work, Kambe uses a palladium catalyst to first insert into the C–S bond of thioesters **195**; then, the alkyne **194** inserts into this bond, and reductive elimination yields the substituted olefins **196** as products in moderate to good yields (figure 4.1.1).



194 **195** **196**

Fig. 4.1 The insertion of alkynes into thioesters.[126]

The Kambe group have published numerous papers on the insertion of alkynes into thioesters.[126-131] Interestingly, their research has also shown that the reaction can include decarbonylation to give the thio-substituted olefins **197**, shown in figure 4.2. This change in reaction pathway can be achieved by using a platinum tetrakis catalyst instead of palladium.[129-131]



R^1 = CO_2Et, CH_2OMe
CH_2OPh, CH_2OAc

197

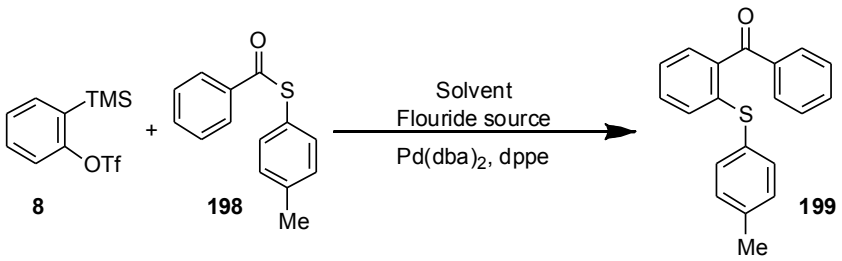
Fig. 4.2 The platinum catalysed decarbonylative insertion of alkynes into thioesters.[129]

The above work provided us with a suitable starting point to begin our investigations into the insertion of arynes into thioesters. The fact that there was precedence for a similar reaction was encouraging, and furthermore the decarbonylative variation of the reaction was interesting enough to also warrant some investigation.

4.1 Reaction Optimisation

It was decided to begin our investigations on the insertion of arynes into thioesters using conditions similar to those described in the amide insertion project, previously conducted in the group.[125] The first attempts at the reaction were all conducted using thioester **198** and benzyne precursor **8** as starting materials, with the hope of making the insertion product **199**.

The first reactions investigated used no catalyst under conditions similar to those published on the work on amide insertions. It was quickly found however, that no insertion occurred without catalysis. It was then decided to try conditions similar to those published by Kambe and co-workers, where a $Pd(dba)_2$/dppe catalytic system was employed.

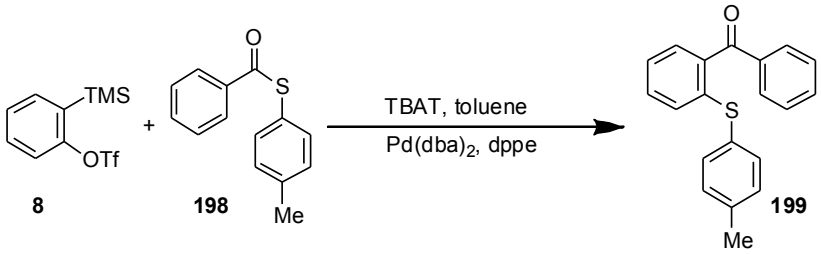


Entry	Temp	Solvent	Fluoride source	Yield (%)[a]
1	RT	MeCN	CsF	0
2	50 °C	MeCN	CsF	0
3	90 °C	MeCN:toluene 1:3	CsF	trace
4	110 °C	MeCN:toluene 1:3	CsF	15
5	110 °C	toluene	TBAT	35

Table 4.1.1. Reaction optimisation of benzyne insertion into thioester **198**. Reaction conditions: Benzyne precursor **8** (90 mg, 0.3 mmol, 1 equiv.), thioester **198** (103 mg, 0.45 mmol, 1.5 equiv.), solvent (2 mL), fluoride source (3 equiv.), $Pd(dba)_2$ (8.6 mg, 0.015 mmol, 5 mol%) and dppe (7.2 mg, 0.018 mmol, 6 mol%) were heated together O/N in a sealed carousel tube. [a] Isolated yields.

Using the thioester in excess, a variety of different solvents, temperatures and fluoride sources were tried. It was found that the reaction would only proceed at temperatures above 110 °C (Entries 4–5), and that a toluene solvent system with TBAT as a fluoride source was the best choice for the reaction. The reaction was made to go in

35% yield under these conditions, and further screening of catalyst loading and concentration was then performed (table 4.1.2.).

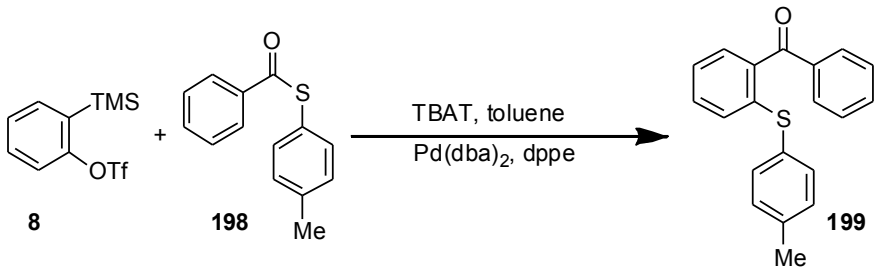


Entry	mol % catalyst	Volume of toluene (mL)	Yield (%)[a]
1	15	2	10
2	10	2	16
3	5	2	34
4	2.5	2	42
5	1	2	49
6	0.5	2	36
7	0.25	2	23
8	0	2	0
9	1	1	42
10	1	3	31

Table 4.1.2. Reaction optimisation of benzyne insertion into thioester **198**. Reaction conditions: Benzyne precursor **8** (90 mg, 0.3 mmol, 1 equiv.), thioester **198** (103 mg, 0.45 mmol, 1.5 equiv.), toluene, TBAT (324 mg, 0.6 mmol, 2 equiv.), $Pd(dba)_2$ and dppe were heated together at 110 °C O/N in a sealed carousel tube. [a] Isolated yields.

It was found there was an optimum catalyst loading for the reaction – 1 mol% of catalyst and ligand gave a 49% yield of product (Entry 5). The screen of concentration found that the solvent volume of 2 mL was the best for the reaction.

We next investigated possible alternate solvents for the reaction; unfortunately, none of these gave increased yields over toluene (table 4.1.3.). It was found that solvents similar to toluene such as benzene, xylene and mesitylene also gave good yields (entries 1–3) but more polar solvents such as DMF, dioxane and DME were not viable for the reaction (Entries 4–6).

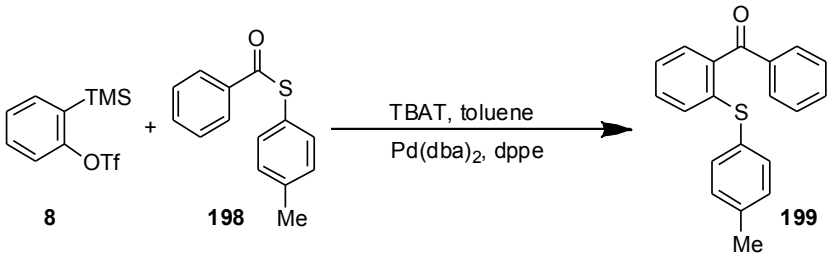


Entry	Solvent	Yield (%)[a]
1	benzene	45
2	xylene	39
3	mesitylene	31
4	DMF	0
5	dioxane	trace
6	DME	0

Table 4.1.3. Reaction optimisation of benzyne insertion into thioester **198**. Reaction conditions: Benzyne precursor **8** (90 mg, 0.3 mmol, 1 equiv.), thioester **198** (103 mg, 0.45 mmol, 1.5 equiv.), toluene (2 mL), TBAT (324 mg, 0.6 mmol, 2 equiv.), $Pd(dba)_2$ (1.7 mg, 0.03 mmol, 1 mol%) and dppe (1.4 mg, 0.033 mmol, 1.2 mol%) were heated together at 110 °C O/N in a sealed carousel tube. [a] Isolated yields.

With little headway being made through this reaction optimisation it was decided to pursue another course. A new set of reaction optimisations which placed the thioester as the limiting reagent in the reaction was conducted. As catalyst loading was found to be the key parameter in previous screens this was the first parameter investigated.

It was again found that there was an optimum catalyst and ligand loading for the reaction (table 4.1.4.). In this instance, the optimum loading was 3 mol% which gave an improved yield of 61%. Reactions were screened using 1.5 equivalents of benzyne precursor. It was found that 1.1 equivalents of benzyne precursor in the reaction was not enough (entry 7), and that extra benzyne precursor had no positive effect on the reaction and only served to complicate purification (entry 6). Concentration and microwave chemistry were also investigated in this screen (entries 8–12). It was found that performing the reaction in the microwave was not beneficial to the reaction and that 3 mL of toluene was the optimum solvent volume.

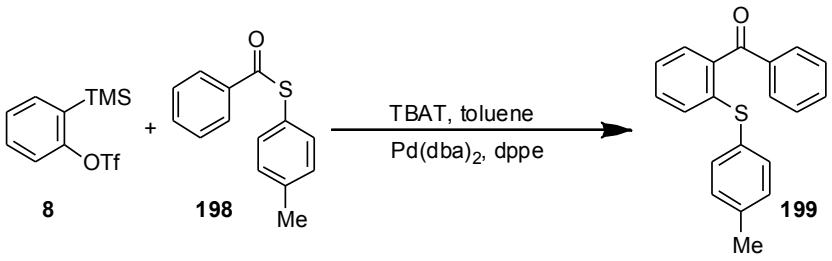


Entry	mol % catalyst	Volume of toluene (mL)	Yield (%)[a]
1	1	3	31
2	2	3	49
3	3	3	61
4	4	3	54
5	5	3	32
6[b]	3	3	45
7[c]	3	3	31
8	3	2	51
9	3	4	55
10[d]	3	3	46
11[e]	3	3	35

Table 4.1.4. Reaction optimisation of benzyne insertion into thioester **198**. Reaction conditions: Benzyne precursor **8** (101 µL, 0.375 mmol, 1.5 equiv.), thioester **198** (57 mg, 0.25 mmol, 1 equiv.), toluene, TBAT (425 mg, 0.75 mmol, 3 equiv.), $Pd(dba)_2$ and dppe were heated together at 110 °C O/N in a sealed carousel tube. [a] Isolated yields. [b] 3 equiv of benzyne precursor was used. [c] 1.1 equiv. of benzyne precursor was used. [d] Reaction performed at 120 °C for 5 min in the microwave. [e] Reaction performed at 140 °C for 5 min in the microwave.

The success obtained using an excess of benzyne precursor led us to investigate our ligand choice. A screen of 12 ligands was set up which is detailed in table 4.1.5.

The reaction screen found that the xanthene and dppp ligands did not work well in the reaction (entries 1 & 3) – the larger bite angles of these ligands may be the cause of the lower yields. Many of the mono and bi-dentatate phosphine ligands (entries 2, 5–7 & 10) worked a little giving yields of >30% but none could achieve yields anywhere near that of the dppe used in the earlier screens. Interestingly, the reaction actually works without ligand giving a reasonable 29% yield.



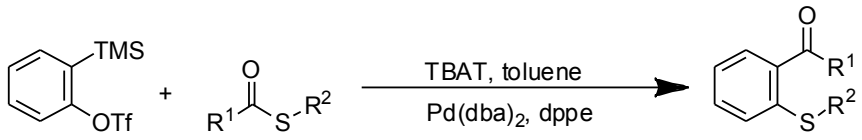
Entry	ligand	Yield (%)[a]
1	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene	16
2	rac-2-(di-*tert*-butylphosphino)-1,1'-binapthyl	32
3	dppm	25
4	dppp	12
5	tricyclohexylphosphine	32
6	JohnPhos	32
7	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl	35
8	rac-BINAP	20
9	1,10-phenanthroline	20
10	triphenylphosphine	35
11	No ligand	29

Table 4.1.5. Reaction optimisation of benzyne insertion into thioester **198**. Reaction conditions: Benzyne precursor **8** (101 µL, 0.375 mmol, 1.5 equiv.), thioester **198** (57 mg, 0.25 mmol, 1 equiv.), toluene (3 mL), TBAT (425 mg, 0.75 mmol, 3 equiv.), $Pd(dba)_2$ (4.2 mg, 7.5 µmol, 3 mol%) and ligand were heated together at 110 °C O/N in a sealed carousel tube. [a] Isolated yields.

With the ligand screen not offering any better conditions than those developed in table 4.1.4, the reaction screening for this reaction was considered complete. Using the conditions detailed in entry 3, table 4.1.4 the substrate scope of the reaction was explored.

4.2 Exploring the Scope of the Reaction

The reaction scope was first explored with respect to the thioester substitution patterns. The results of the screen are detailed in table 4.2.1. below.



8 **200** **201**

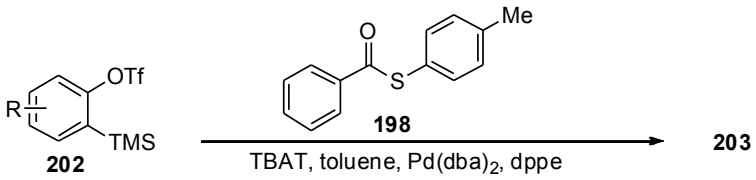
Entry	R^1	R^2	Product	Yield (%)[a]
1	Ph	Ph	**201a**	62
2	Ph	*p*-MeC_6H_4	**201b**	61
3	Ph	*p*-FC_6H_4	**201c**	49
4	Ph	*p*-ClC_6H_4	**201d**	43
5	Ph	*p*-$OMeC_6H_4$	**201e**	25
6	Ph	*p*-BrC_6H_4	**201f**	0
7	Ph	*p*-$NO_2C_6H_4$	**201g**	0
8	Ph	Et	**201h**	0
9	Ph	t-Bu	**201i**	0
10	*p*-MeC_6H_4	Ph	**201j**	53
11	*p*-FC_6H_4	Ph	**201k**	42
12	*p*-ClC_6H_4	Ph	**201l**	34
13	2-naphthyl	Ph	**201m**	23
14	*p*-$NO_2C_6H_4$	Ph	**201n**	0
15	*p*-$CF_3C_6H_4$	Ph	**201o**	0
16	t-Bu	Ph	**201p**	0
17	Et	Ph	**201q**	0

Table 4.2.1. Exploring the scope of benzyne insertion into thioesters. Reaction conditions: Benzyne precursor **8** (101 μL, 0.375 mmol, 1.5 equiv.), thioester **200** (0.25 mmol, 1 equiv.), toluene (3 mL), TBAT (425 mg, 0.75 mmol, 3 equiv.), $Pd(dba)_2$ (4.2 mg, 7.5 μmol, 3 mol%) and dppe (4.2 mg, 0.099 mmol, 3.6 mol%) were heated together at 110 °C O/N in a sealed carousel tube. [a] Isolated yields.

It was found that some of the less reactive aromatic substituents were tolerated on both sides of the thioester linkage in the reaction. The unsubstituted phenyl as well as the *para*-substituted chloro, fluoro and methoxy derivatives all reacted to give

moderate to good yields (entries 1–5, 11–13). In addition to this, the more sterically challenging naphthyl derivative **200m** was found to work giving a modest yield of 23%. It was found that the more reactive *p*-bromo-phenyl derivatives did not work in the reaction (entry 6) and it is thought that this may be due to the palladium species oxidatively adding to the C–Br bond. The electron poor nitro- and trifluoromethyl-substituted aromatic rings did not work well yielding none of the desired insertion product in the reaction (entries 7, 8, 15 & 16). Non-aromatic substituents were entirely inert under the reaction conditions giving only starting materials and triphenylene in these reactions (entries 9, 10, 17 & 18).

With the reaction scope of the thioesters thoroughly examined, we next turned our attention to investigating the substrate scope of arynes (table 4.2.2.). It was found that the simple methyl substituted aryne **202a** worked well in the reaction giving a moderate yield of 35% with a 48:52 ratio of the two possible regioisomers (entry 1). Similarly, the phenyl derivative also worked, albeit in a very messy reaction which resulted in no pure product being obtained. The simple naphthyne derivative **202b** also worked but again in a poor yield of only 11%. Bromine substituted arynes were not at all viable in the reaction (entries 4 & 5), and it is thought that this could again be due to the oxidative addition of palladium into the C–Br bond interfering with the reaction.



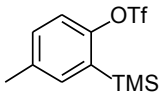
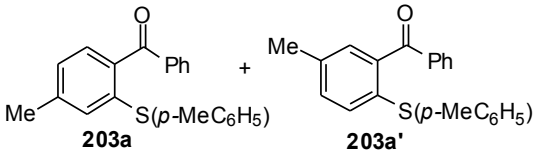
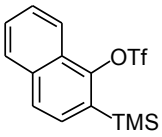
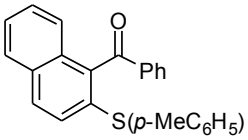
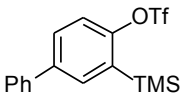
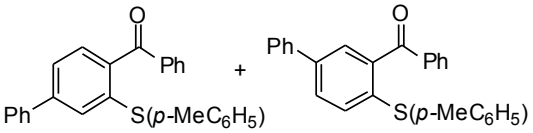
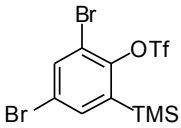
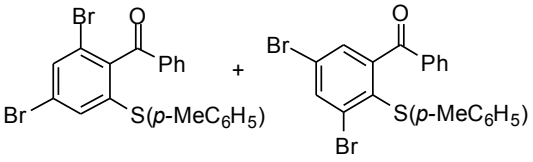
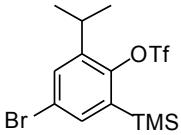
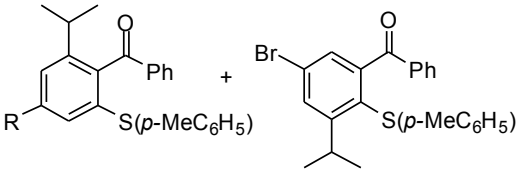
Entry	starting material	Products	yield (%)[a]
1	 **202a**	 **203a** **203a'**	35[b]
2	 **202b**	 **203b**	11
3	 **202c**	 **203c** **203c'**	<20
4	 **202d**	 **203d** **203d'**	0
5	 **202e**	 **203e** **203e'**	0

Table 4.2.2. Exploring the scope of arynes **202** for the insertion into thioester **198**. Reaction conditions: Benzyne precursor **202** (0.375 mmol, 1.5 equiv.), thioester **198** (57 mg, 0.25 mmol, 1 equiv.), toluene (3 mL), TBAT (425 mg, 0.75 mmol, 3 equiv.), $Pd(dba)_2$ (4.2mg, 7.5 μmol, 3 mol%) and dppe (4.2 mg, 0.099 mmol, 3.6 mol%) were heated together at 110 °C O/N in a sealed carousel tube. [a] Isolated yields. [b] Isolated as a 48:52 mixture of the two possible regioisomers.

Overall, the substrate scope for the reaction was found to be rather poor. Yields were moderate to good at best and most substitutions on either of the starting materials were not well tolerated. It was decided to move on at this point and investigate the decarbonylative insertion reaction and the insertion into esters.

4.3 Investigating the Decarbonylative Reaction

The next reaction we decided to investigate was the decarbonylative aryne insertion into thioesters based on the work by Kambe and co-workers[129] as depicted in figure 4.1.2. A proposed mechanism for the decarbonylative aryne procedure is illustrated in figure 4.3.1. The reaction begins with platinum insertion into the C–S bond of the thioester to give **204**. This platinum complex has been shown previously by Kambe to undergo decarbonylation to give complex **205**. The difficult steps in the mechanism were envisaged to be the insertion of benzyne into Pt–S bond followed by reductive elimination to give the product **207**. Kambe utilises an oxygen atom attached to the *β*-position of the alkyne to achieve coordination to the platinum metal. This coordination facilitates the insertion of the alkyne into the platinum complex. As there is no coordinating atom in benzyne, it was anticipated that this step may prove to be problematic.

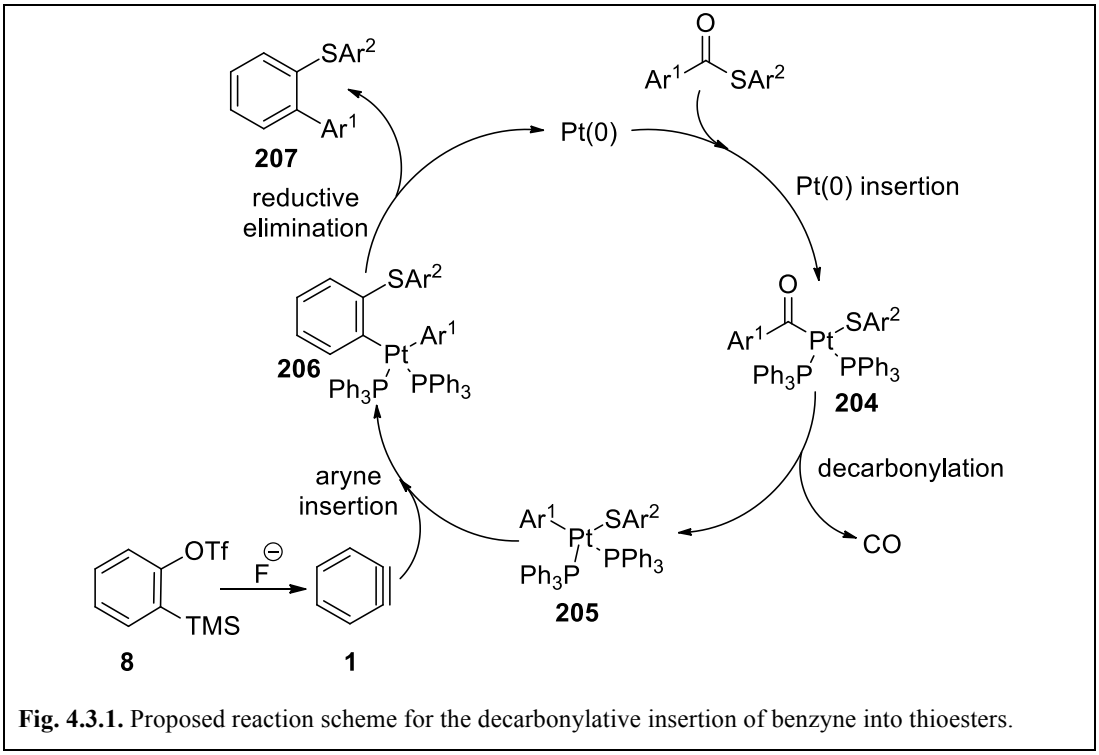


Fig. 4.3.1. Proposed reaction scheme for the decarbonylative insertion of benzyne into thioesters.

It was decided to screen a variety of reaction conditions to see if the reaction could be made to work with arynes. Although the benzyne did not have additional coordinating atoms to coordinate with the platinum species **205**, it was hoped that this could be compensated for by the increased reactivity of benzyne over alkynes.

A variety of different temperatures (RT – 140 °C), solvents (MeCN, toluene, mesitylene) and fluoride sources (caesium fluoride, TBAT) were investigated using $Pt(PPh_3)_4$ as catalyst. Unfortunately, none of these reactions yielded the desired products. It was thought that this was due to the aryne insertion not occurring due to the lack of coordinating groups on the benzyne. It was decided that no further work was to be done on this reaction and we decided to investigate the aryne insertion into esters.

4.4 Aryne Insertion into Esters

The aryne insertion into esters was found to be unsuccessful. Conditions similar to those used for thioester insertion were tried, both with and without palladium catalyst, and resulted only in recovery of the ester starting material. It is thought that this could be due to esters not being as viable for the palladium insertion into the C–O bond.

4.5 Conclusions

The palladium catalysed insertion of arynes into thioesters was found to be successful. It was found that the reaction did not proceed in the absence of catalyst but required a specific stoichiometry of a Pd/dppe catalyst. Yields were found to be moderate to good for a limited set of substrates and it was generally found that the scope of this reaction was poor with many examples giving negative results.

Similar reactions were tried with a decarbonylative aryne insertion into thioesters and an insertion of arynes into esters. Both of these reactions did not yield any of the desired products and were deemed unsuccessful.

5 A Benzyne Ene Reaction

There is large precedent in the literature for aryne insertion into sigma bonds.[27, 125] The common requirement for these reactions is a substrate containing both an electrophilic and nucleophilic component, which is connected through a sigma bond. The nucleophilic component of the molecule initiates the reaction with a nucleophilic attack on the electrophilic benzyne. The resulting zwitterion then rearranges to give a disubstituted aromatic ring as illustrated in figure 5.1.

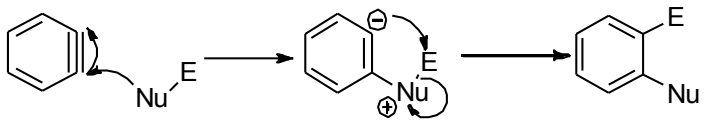


Fig. 5.1. Aryne insertion into sigma bonds.

In many instances, the electrophilic part of the molecule is a carbonyl group and insertion into amides,[82, 125] sulfinamides,[82] ureas,[132] acid chlorides,[84] β-ketophosphonates,[133] β-dicarbonyl,[79] α-cyanocarbonyl[80] and β-ketoesters[83, 134] can be achieved. It was decided to investigate the possible insertion reaction of benzyne into 2-anilinopyridine **208**. It was hypothesised that the 1–2 double bond of pyridine could act as the electrophilic component of the molecule, in a similar way to a carbonyl group, and that the amine would act as the nucleophile. The mechanism would follow the pathway illustrated in figure 5.2. to give the product **209**. It was thought that the reaction pathway might have to compete with straightforward nucleophilic addition of the amine – a possible side reaction which would give aniline **210**.

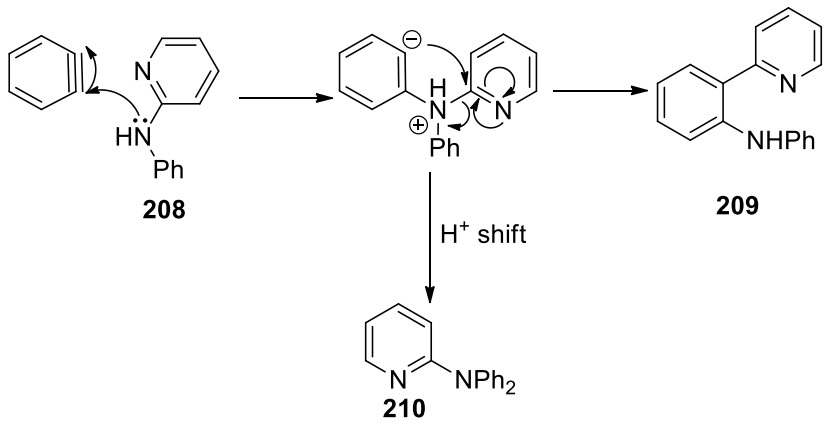


Fig. 5.2. Postulated mechanism for aryne insertion into the C–N bond of 2-anilino pyridine **208**.

5.1 Results and Discussion

A reaction screen was set up and it was quickly found that new products were observed on the TLC plate. Upon analysis of these samples it was discovered that neither the desired insertion product **209**, nor the nucleophilic addition product **210** was formed. Instead, a product which showed a proton in the NMR region of 5–6 ppm was isolated. Intrigued at the presence of olefinic protons in our spectrum, we investigated the product further and found that we had actually formed the imine product **211**. This product could have been made *via* an unexpected ene-reaction of the anilino-pyridine. (see figure 5.1.1.).

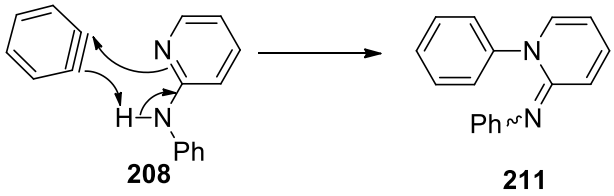


Fig. 5.1.1. An ene reaction between benzyne and 2-anilinopyridine **208**.

A very quick reaction screen was set up and after a few reactions excellent conditions were achieved. When the reaction was performed in acetonitrile at room temperature with 3 equivalents of amine and caesium fluoride, it yielded 91% of **211** in a 4:1 ratio of possible stereoisomers. The stereoisomers could be easily separated and were highly coloured compounds due to their conjugated nature.

Upon research of the literature, it was found that there was no precedent for the ene reaction of 2-aminopyridines. However, similar work was published on the reaction of pyridone **213** with benzyne using anthranilic acids as benzyne precursors.[135, 136] The main products from the reaction were **215**, which was formed *via* an ene-reaction and the Diels-Alder product **216**. These were isolated in 35% and 7% yields respectively. However, it was found that a 4% yield of 1-phenyl-2-pyridone **214** was formed as by-product in the reaction (figure 5.1.2). This product was formed *via* an ene process of the 2-pyridol tautomer **212** in an analogous reaction to that which we observed with 2-aminopyridines.

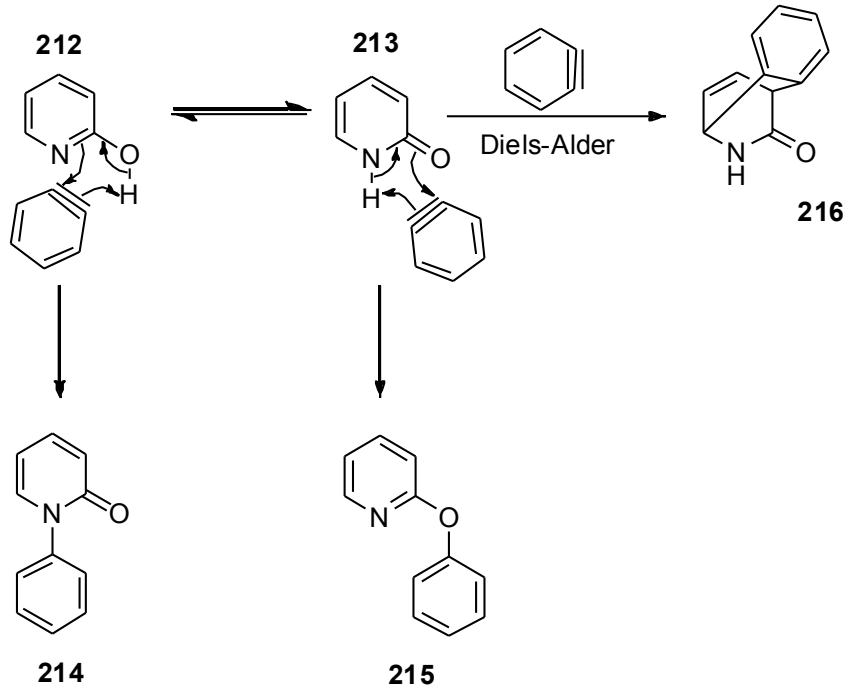


Fig. 5.1.2. The reactions of pyridone **203** with benzyne.

With this literature in mind the reaction with pyridone was then tried using the conditions developed for the anilino-pyridine example. It was found that under our conditions a 37% yield of the desired **214** was formed in addition to a 35% of the by-product **215**.

5.2 Conclusions

This project will be continued by another member of the group. The scope of 2-amino pyridines will first be tested, which will then be followed by an investigation of which functional groups are tolerated when placed in the 2-position of the pyridine ring. It is envisaged that functional groups such as thiols and even methyl groups might work well in the reaction. In addition to this, the ene reaction does not have to proceed with the removal of a proton; any suitable leaving group may also be employed which would give interesting disubstituted arene products (see figure 5.2.1.).

The ene reaction with pyridone will also be further investigated. It is thought that with suitable reaction optimisation this reaction may be made to proceed more selectively in the direction of the ene reaction.

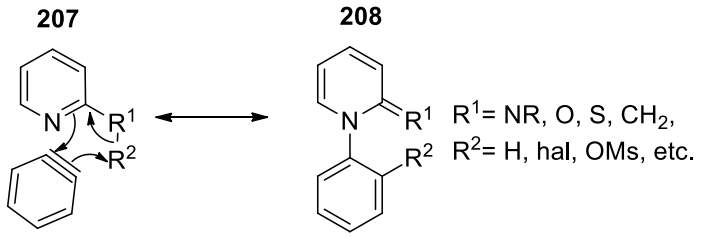


Fig. 5.2.1. An illustration of the possible scope for the ene reaction.

6 Experimental

6.1 General Experimental Data

All nuclear magnetic resonance were recorded using either 360 MHz, 400 MHz or 500 MHz Bruker Advance spectrometers. Unless otherwise stated, deuterochloroform was used as the solvent with tetramethylsilane as the internal standard. Chemical shifts were recorded in parts per million (δ) and all coupling values are in Hertz. The following abbreviations were used when referring to peak shape:

s- singlet
d- doublet
dd- doublet of doublets
dt- doublet of triplets
m- multiplet
q- quartet
Q- quaternary
t- triplet

All reactions, unless otherwise stated were performed using oven dried glassware and under an inert atmosphere of dry nitrogen and all chromatography columns were packed with strata SI-1 Silica (55µm, 70Å). All commercially available reagents were used as received, without purification.

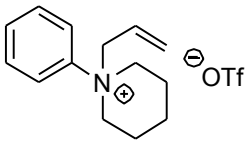
All infrared spectroscopy experiments were performed using a Jas.Co FT/IR-460 plus Fourier Transform Infrared Spectrometer using sodium chloride plates to load the sample.

All accurate mass spectrometry experiments were carried out by the EPRSC mass spectrometry service in Swansea. Accurate mass Electron Ionisation (EI) and Chemical Ionisation (CI) measurements, in positive ionisation mode, were obtained on the MAT95 by "peak matching", with mass resolution between 8000 and 10 000 (10% valley definition). For EI, Heptacosa (perfluorotributylamine) is the usual reference compound, and for CI, PEG (polyethyleneglycol) is usually used.

Electrospray ionisation (ESI) analysis were aquired on the orbitrap using nanospray in both positive and negative ion modes

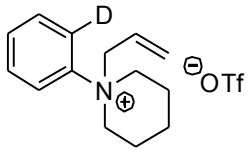
6.2 Experimental Data for the Benzyne Aza-Claisen Reaction

1-Allyl-1-phenyl-piperidinium triflate 108a



1-Allylpipiridine (37 mg, 0.3 mmol, 1.5 equiv), caesium fluoride (91 mg, 0.6 mmol, 3 equiv.), toluene (0.75 mL) and acetonitrile (0.25 mL) were placed in a sealed carousel tube under nitrogen. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (60 mg, 0.20 mmol, 1 equiv.) was then added and the reaction was stirred at room temperature for 48 h. The reaction was then filtered and evaporated to dryness. The compound was then dry loaded onto a chromatography column and purified using DCM/methanol (0-5%) to give the product as a colourless oil (50 mg, 71%). ^{1}H NMR 360 MHz δ_H, 7.67-7.48 (5H, m), 5.88 (2H, tdd, J=7.0, 10.1, 17.1), 5.52 (1H, m), 4.43 (2H, d, J=13.3), 4.35 (2H, d, J=7.0), 3.96 (2H, t, J=12.7), 1.96-1.90 (2H, m), 1.76-1.66 (2H, m); ^{13}C NMR, 90 MHz δ_C 139.1 (**Q**), 130.9 (**C**H), 130.3 (**C**H), 129.6 (**C**H_2), 123.7 (**C**H), 122.4 (**C**H), 73.6 (CH_2), 60.6 (**C**H_2), 21.3 (**C**H_2), 20.8 (**C**H_2); ^{19}F NMR, 250 MHz δ_F -79.64 (3H, s, C**F**$_3$); IR (film/cm^{-1}) 3568, 2954, 1597, 1491, 1261, 1030, 638, 519; HRMS (EI$^+$) calc for $(C_{14}H_{20}N)^+$: $(M)^+$ 202.1588. Found 202.1599. HRMS (EI$^+$) calc for $(2(C_{14}H_{20}N)^+ (CF_3O_3S)^-)$cluster $(M)^+$ 553.2706. Found 553.2696.

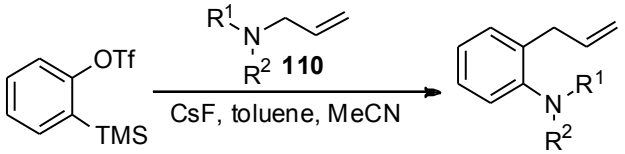
Deuterated 1-Allyl-1-phenyl-piperidinium triflate 108b



The general procedure was followed as above with the exception of using deuterated acetonitrile instead of acetonitrile to give 50 mg of product as a colourless oil. 71% yield. ^{1}H NMR, 360 MHz δ_H 7.66-7.58 (3H, m), 7.54-7.47 (1H, m), 5.58-5.45 (2H, m), 5.45-5.32 (1H, m), 4.42 (2H, d, J=13.2), 4.35 (2H, d, J=7.0) 3.95 (2H, t, J=12.4), 1.94 (2H, d, J=13.6), 1.80-1.60 (4H, m); ^{2}H NMR, 250 MHz δ_D 7.64 (1H, s); ^{13}C

NMR, 90 MHz δ_C 139.0 (**Q**), 130.9 (2**C**H), 130.2 (**C**D, t, J= 56.5), 130.2 (**C**H), 129.6 (**C**H_2), 123.7 (**C**H), 122.3 (**C**H), 119.0 (**C**), 73.6 (**C**H_2), 60.6 (**C**H_2), 21.3 (**C**H_2), 20.8 (**C**H_2); IR (film/cm^{-1}) 3502, 3018, 1457, 1242, 1162, 1030. HRMS (EI) calc for $C_{14}H_{19}ND$: 203.16530. Found 203.16513.

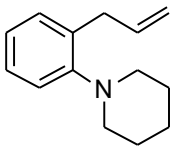
General Procedure for the Benzyne Aza-Claisen Reaction



8 **111**

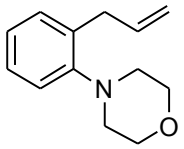
The allyl amine **110** (0.3 mmol, 1.5 equiv.), caesium fluoride (91 mg, 0.6 mmol, 3 equiv.), toluene (0.75 mL) and acetonitrile (0.25 mL) were placed in a sealed carousel tube under nitrogen. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate **8** (60 mg, 0.20 mmol, 1 equiv.) was then added and the reaction was heated to 110 °C for 48 h. The reaction was then filtered and concentrated *in vacuo* to give a crude product which was then purified by column chromatography (SiO_2, hexanes, dry loading).

1-(2-Allylphenyl) piperidine 111a



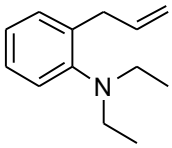
55.5 mg isolated as a colourless oil. 92% yield. ^{1}H NMR 360 MHz δ_H 7.23 – 7.17 (2H, m), 7.08 (1H, dd, J=1.3, 7.9), 7.03 (1H, dt, J=1.3, 7.4), 6.01 (1H, tdd, J=6.6, 10.0, 16.7), 5.16 – 5.07 (2H, m), 3.49 (2H, d, J=6.6), 2.85 – 2.82 (4H, m), 1.75 – 1.69 (4H, m), 1.61 – 1.54 (2H, m); ^{13}C NMR 90 MHz δ_C 152.7 (Q), 138.0 (Q), 134.9 (CH), 129.8 (CH), 126.7 (CH), 123.1 (CH), 119.7 (CH), 115.4 (CH_2), 54.0 ($2CH_2$), 34.8 ($2CH_2$), 26.5 (CH_2), 24.3 (CH_2); IR (film/cm^{-1}) 2933, 2853, 2800, 1489, 1450, 1226; HRMS (EI^+) calc for $C_{14}H_{19}N$: $(M)^+$ 201.1512. Found: 201.1510.

1-(2-Allylphenyl)morpholine 111b



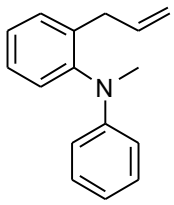
37.8 mg isolated as a colourless oil. 62% yield. ^{1}H NMR, 360 MHz δ_H 7.27-7.20 (2H, m), 7.14-7.06 (2H, m), 6.00 (1H, m), 5.15-5.06 (2H, m), 3.86 (4H, t, J=4.5), 3.52 (2H, d, J=6.5), 2.92 (4H, t, J=4.5); ^{13}C NMR, 90 MHz δ_C 151.1 (**Q**), 137.8 (**C**H), 135.0 (**Q**), 130.2 (**C**H), 127.0 (**C**H), 124.0 (**C**H), 119.9 (**C**H), 115.7 (**C**H_2), 67.4 (2**C**H_2), 52.9 (2**C**H_2), 34.8 (**C**H_2); IR (film/cm^{-1}) 2958, 2852, 1490, 1450, 1224, 1118, 917, 765; HRMS (EI$^+$) calc for $C_{13}H_{17}NO$: $(M)^+$ 203.1305. Found: 203.1305.

(2-Allylphenyl)diethylamine 111c



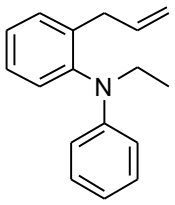
The general procedure was followed with the exception that the reaction was stirred for 24 h at RT prior to heating to reflux, affording 36.9 mg of product as a colourless oil. 65% yield. ^{1}H NMR, 360 MHz δ_H 7.25-7.18 (2H, m), 7.14 (1H, m), 7.06 (1H, dt, J=1.6, 7.2), 5.99 (1H, tdd, J=6.6, 10.0, 16.9), 5.08 (2H, m), 3.53 (2H, d, J=6.6), 2.98 (4H, q, J=7.1), 0.99 (6H, t, J=7.1). ^{13}C NMR, 90 MHz δ_C 149.6 (**Q**), 138.1 (**C**H), 137.6 (**Q**), 129.9 (**C**H), 126.4 (**C**H), 123.7 (**C**H), 122.8 (**C**H), 115.2 (**C**H_2), 48.3 (2**C**H_2), 34.9 (**C**H_2), 12.6 (2**C**H_3). IR (film/cm^{-1}) 2972, 1491, 1238, 910, 764. HRMS (ESI$^+$) calc for $C_{13}H_{19}NH^+$: $(M + H)^+$ 190.1590. Found: 190.1588.

(2-Allyl-phenyl)-methyl-phenyl-amine 111d



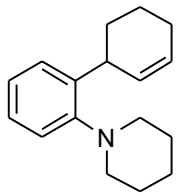
61.0 mg isolated as a colourless oil. 91% yield. ^{1}H NMR, 360 MHz δ_H 7.48-7.23 (6H, m), 6.82 (1H, qt, J=1.0, 7.3), 6.67-6.62 (2H, m), 6.00 (1H, dtdd, J=1.0, 6.7, 10.2, 15.9), 5.12 (2H, m), 3.39 (2H, d, J=6.8), 3.32 (3H, s); ^{13}C NMR, 90 MHz δ_C 149.3 (**Q**), 146.5 (**Q**), 138.9 (**Q**), 136.9 (**C**H), 130.4 (**C**H), 128.9 (2**C**H), 128.5 (**C**H), 128.0 (**C**H), 126.6 (**C**H), 116.8 (**C**H), 115.8 (**C**H_2), 112.8 (2**C**H), 39.6 (**C**H_3), 35.4 (**C**H_2). The spectroscopic data was in agreement with that previously published.[137]

(2-Allyl-phenyl)-ethyl-phenyl-amine 111e



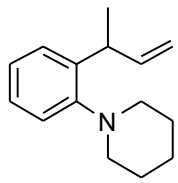
50.5 mg of product isolated as a colourless oil. 71% yield. ^{1}H NMR, 360 MHz δ_H 7.38 (1H, m), 7.33-7.27 (2H, m), 7.22-7.15 (3H, m), 6.71 (1H, tt, J=1.0, 7.3), 6.57-6.51 (2H, m), 5.91 (1H, tdd, J=6.8, 10.5, 17.2), 5.05 (2H, m), 3.68 (2H, q, J=7.1), 3.31 (2H, td, J=6.8, 1.3), 1.26 (3H, t, J=7.1); ^{13}C NMR, 90 MHz δ_C 148.4 (**Q**), 144.6 (**Q**), 139.3 (**Q**), 136.8 (**C**H), 130.4 (**C**H), 129.9 (**C**H), 128.9 (2**C**H), 127.7 (**C**H), 126.6 (**C**H), 116.4 (**C**H), 116.0 (**C**H_2), 112.8 (2**C**H), 45.9 (**C**H_2), 35.1 (**C**H_2), 12.5 (**C**H_3); IR (film/cm^{-1}) 2926, 2853, 1592, 1498, 1268, 746. HRMS (ESI$^+$) calc for $C_{17}H_{19}NH^+$: $(M+H)^+$ 238.1590. Found: 238.1590.

(2-Cyclohex-2-enyl-phenyl)-methyl-phenyl-amine 111f



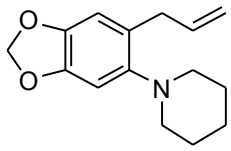
53.5 mg of product isolated as a colourless oil. 74% yield. ^{1}H NMR, 360 MHz δ_H 7.26-7.05 (4H, m), 5.92-5.85 (1H, m), 5.66-5.60 (1H, m), 4.05-3.97 (1H, m), 2.92-2.74 (4H, m), 2.20-1.98 (3H, m), 1.90-1.48 (9H, m); ^{13}C NMR, 90 MHz δ_C 152.6 (**Q**), 142.3 (**Q**), 131.5 (**C**H), 128.5 (**C**H), 127.5 (**C**H), 126.4 (**C**H), 123.8 (**C**H), 120.5 (**C**H), 54.8 (**C**H_2), 35.4 (**C**H), 31.8 (**C**H_2), 26.7 (**C**H_2), 25.0 (2**C**H_2), 25.0 (**C**H_2), 24.3 (**C**H_2), 21.9 (**C**H_2); IR (film/cm^{-1}) 3018, 2931, 2854, 2790, 1487, 1449, 1224; HRMS (EI$^+$) calc for $C_{17}H_{23}N$: $(M)^+$ 241.1825. Found: 241.1825.

1-[2-(1-Methyl-allyl)-phenyl]-piperidine 111g



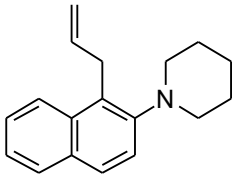
The general procedure was followed with the exception that the reaction was performed in refluxing DME. 20 mg of product was isolated as a colourless oil. 31% yield. ^{1}H NMR, 360 MHz δ_H 7.22-7.02 (4H, m), 6.04 (1H, ddd, J=6.0, 10.3, 17.2), 5.03 (1H, td, J=1.7, 20.3), 5.01 (1H, td, J=1.7, 13.5), 4.14 (1H, m), 2.90-2.70 (4H, m) 1.80-1.64 (4H, m), 1.62-1.50 (2H, m), 1.31 (3H, d, J=7.0); ^{13}C NMR, 90 MHz δ_C 152.4 (**Q**), 144.1 (C**H**), 141.3 (**Q**), 127.7 (**C**H), 126.5 (**C**H), 123.9 (**C**H), 120.5 (**C**H), 112.4 (=**C**H_2), 54.7 (2**C**H_2), 35.8 (**C**H), 26.7 (2**C**H_2), 24.4 (**C**H_2), 21.0 (**C**H_3); IR (film/cm^{-1}) 2933, 2792, 1487, 1448, 1224, 909, 752. HRMS (EI$^+$) calc for $C_{15}H_{21}N$: $(M)^+$ 215.1669. Found: 215.1666.

1-(6-Allyl-benzo[1,3]dioxol-5-yl)-piperidine 111j



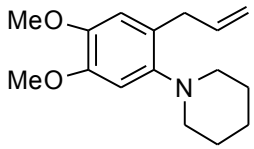
The general procedure was followed using DCM/hexane as the chromatography eluent, affording 42 mg of the product as a colourless oil. 57% yield. ^{1}H NMR, 360 MHz δ_H 6.71 (1H, s), 6.70 (1H, s), 6.00-5.89 (1H, m), 5.89 (2H, s), 5.12-5.02 (2H, m), 3.45 (2H, d, J=6.6), 2.73 (4H, t, J=6.6), 1.74-1.64 (4H, m), 1.60-1.48 (2H, m); ^{13}C NMR 90 MHz δ_C 146.0 (**Q**), 138.3 (**C**H), 128.5 (2**Q**), 115.2 (**C**H_2), 109.4 (**C**H), 101.9 (**C**H), 101.9 (**Q**), 100.8 (**C**H_2), 54.6 (2**C**H_2), 34.9 (2**C**H_2), 26.6 (**C**H_2), 24.2 (**C**H_2); IR (film/cm^{-1}) 2934, 1726, 1637, 1483, 1183, 1041, 910. HRMS (EI$^+$) calc for $C_{15}H_{19}NO_2$: (M)$^+$ 245.1410. Found 245.1412.

1-(1-Allyl-naphthalen-2-yl)-piperidine 111k



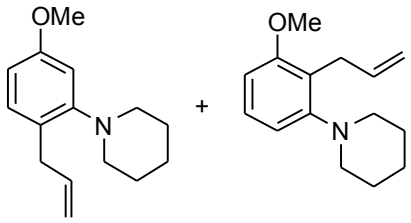
The general procedure was followed on a 0.9 mmol scale to afford 179 mg of the product as a colourless oil. 79% yield. ^{1}H NMR, 360 MHz δ_H 8.03 (1H, d, J=8.5), 7.83 (1H, d, J=8.5), 7.77 (1H, d, J=8.8), 7.53-7.39 (3H, m), 6.12 (1H, tdd, J=5.7, 10.3, 17.1), 5.10-5.00 (2H, m), 4.10 (2H, br), 2.90 (4H, br), 1.76 (4H, br), 1.61 (2H, br); ^{13}C NMR, 90 MHz δ_C 137.8 (**C**), 133.2 (**Q**), 131.0 (**Q**), 129.4 (**Q**), 128.2 (**C**H), 127.5 (**C**H), 127. 5 (**C**H), 125.7 (**C**H), 124.9 (**C**H), 124.1 (**C**H), 120.4 (**C**H), 115.2 (**C**H_2), 54.5 (2**C**H_2), 31.1 (2**C**H_2), 26.7 (**C**H_2), 24.4 (**C**H_2); IR (film/cm^{-1}) 3055, 2933, 2792, 1508, 1371, 1225, 810, 746. HRMS (EI$^+$) calc for $C_{18}H_{22}N$: (M)$^+$ 251.1669. Found: 251.1670.

1-(2-Allyl-4,5-dimethoxy-phenyl)-piperidine 111l



59.6 mg of product isolated as an orange oil. 76% yield. ^{1}H NMR 360 MHz δ_H, 6.71 (1H, s), 6.70, (1H, s), 5.95 (1H, tdd, J=6.6, 10.0, 16.6), 5.13-5.02 (2H, m), 3.86 (3H, s), 3.83 (3H, s), 3.43 (2H, d, J=6.6), 2.77 (4H, t, J=4.9), 1.74-1.62 (4H, m), 1.60-1.50 (2H, m); ^{13}C NMR 90 MHz δ_C 147.4 (**Q**), 145.8 (**Q**), 145.1 (**Q**), 138.3 (**C**H), 127.3 (**Q**), 115.1 (**C**H_2), 113.0 (**C**H), 104.7 (**C**H), 56.1 (**C**H_3), 56.0 (**C**H_3), 54.5 (2**C**H_2), 34.5 (**C**H_2), 26.7 (2**C**H_2), 24.3 (**C**H_2); IR 2933, 1509, 1200, 1112, 1038, 996, 911 HRMS (ESI$^+$) calc for $C_{16}H_{23}NH^+$: $(M+H)^+$ 262.1802. Found: 262.1801.

1-(2-Allyl-5-methoxy-phenyl)-piperidine (111m) &
1-(2-Allyl-3-methoxy-phenyl)-piperidine (111m′)



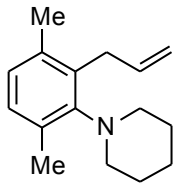
111m **111m'**

The general procedure was followed on a 0.9 mmol scale to give **111m** (orange oil, 73 mg, 55%) and **111m′** (orange oil, 32 mg, 24%).

111m: ^{1}H NMR, 360 MHz δ_H 7.10 (1H, d, J=8.4), 6.64 (1H, d, J=2.6), 6.58 (1H, dd, J=2.6, 8.4), 5.97 (1H, tdd, J=6.3, 10.0, 16.7), 5.16-5.05 (2H, m), 3.79 (3H, s), 3.40 (2H, d, J=6.3), 2.81 (4H, t, J=5.2), 1.78-1.68 (4H, m), 1.63-1.53 (2H, m); ^{13}C NMR, 90 MHz δ_C 158.6 (**Q**), 153.8 (**Q**) 138.4 (**C**H), 130.4 (**C**H), 127.0 (**Q**), 115.1 (**C**H_2), 107.5 (**C**H), 106.5 (**C**H), 55.2 (**C**H_3), 54.0 (2**C**H_2), 34.3 (**C**H_2), 26.5 (2**C**H_2), 24.3 (**C**H_2); IR (film/cm^{-1}) 2934, 1606, 1503, 1198, 1169, 1045, 910. HRMS (EI$^+$) calc for $C_{15}H_{21}N$: $(M)^+$ 231.1618 Found: 231.1621.

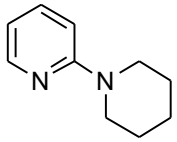
111m′: ^{1}H NMR, 360 MHz δ_H 7.15 (1H, t, J=8.1), 6.74 (1H, d, J=8.1), 6.64 (1H, d, J=8.1), 6.05 (1H, dtdd, J=0.8, 6.2, 10.1, 17.1), 5.08-4.92 (2H, m), 3.81 (3H, s), 3.51 (2H, d, J=6.2), 2.81 (4H, t, J=4.9), 1.76-1.66 (4H, m), 1.62-1.52 (2H, m).; ^{13}C NMR, δ_C 158.5 (**Q**), 154.2 (**Q**), 137.9 (**C**H), 126.9 (**C**H), 123.7 (**Q**), 113.9 (**C**H_2), 112.8 (**C**H), 106.0 (**C**H), 55.5 (**C**H_3), 54.4 (2**C**H_2), 29.7 (**C**H_2), 26.6 (2**C**H_2), 24.4 (**C**H_2); IR (film/cm^{-1}) 2933, 1579, 1468, 1264, 1221, 1121, 733. HRMS (EI$^+$) calc for $C_{15}H_{21}N$: $(M)^+$ 231.1618. Found: 231.1615.

1-(2-Allyl-3,6-dimethyl-phenyl)-piperidine (111n)



The general procedure was followed on a 0.9 mmol scale and 31 mg of the product was isolated as a colourless oil in 15% yield. ^{1}H NMR, 360 MHz δ_H 6.90-6.85 (2H, m,), 5.93 (1H, tdd, J=5.7, 10.2, 17.1), 4.93 (2H, m,), 3.56 (2H, td, J=1.7, 5.7), 3.12 (2H, m), 2.90 (2H, td, J=3.3, 8.2), 2.32 (3H, s), 2.25 (3H, s), 1.75-1.55 (5H, m), 1.42 (1H, m); ^{13}C NMR, 90 MHz δ_C 149.7 (**Q**), 137.7 (**Q**), 136.4 (C**H**), 135.5 (**Q**), 134.9 (**Q**), 129.1 (**C**H), 127.2 (**C**H), 114.2 (**C**H_2), 51.4 (2**C**H_2), 33.2 (**C**H_2), 27.1 (2**C**H_2), 24.7 (**C**H_2), 19.7 (**C**H_3), 19.6 (**C**H_3); IR (film/cm^{-1}) 2929, 1442, 1234, 906, 804. HRMS (EI$^+$) calc for $C_{13}H_{19}N$: 229.1825 $(M)^+$.Found: 229.1823.

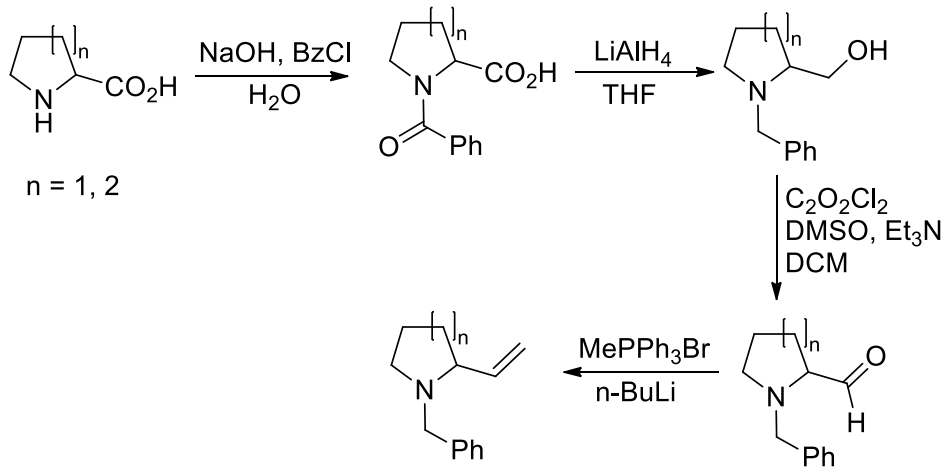
2-Piperidinopyridine 111o



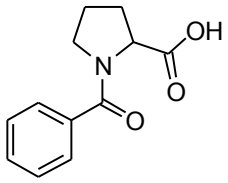
19.4 mg of product isolated as a yellow oil. 40% yield. ^{1}H NMR, 360 MHz δ_H 8.17 (1H, ddd, J=0.8, 2.0, 4.9), 7.44 (1H, m), 6.64 (1H, td, J=0.8, 8.8), 6.55 (1H, ddd, J=0.8, 4.9, 7.1), 3.51 (4H, t, J=4.5), 1.67-1.60 (6H, m); ^{13}C NMR, 90 MHz δ_C 159.65 (**Q**), 147.82 (**C**H), 137.33 (**C**H), 112.36 (**C**H), 107.13 (**C**H), 46.33 (2**C**H_2), 25.50

(2**C**H_2), 24.71 (**C**H_2). The spectroscopic data was in agreement with that previously published.[138]

Synthesis of α-Vinylic Cyclic Amines – Benzylic Derivatives

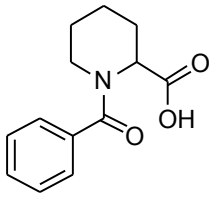


***N*-Benzoyl proline**



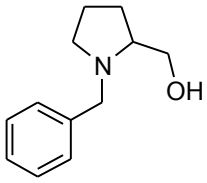
To a 3 necked flask water (45 mL) and sodium hydroxide (1.05 g, 26 mmol, 1 equiv.) were added and the vessel was cooled to 0 ºC. L-proline (3 g, 26 mmol, 1 equiv.) was then added. An additional aliquot of sodium hydroxide (1.05 g, 26 mmol, 1 equiv.) in water (3 mL) was placed in a dropping funnel and benzoyl chloride (3.03 mL, 26 mmol, 1 equiv.) was placed in a second dropping funnel. The contents of both dropping funnels were then added simultaneously and dropwise to the flask before stirring at 0 ºC for 2 h. The mixture was then washed with diethyl ether (2 x 25 mL) before acidifying the aqueous layer with cold 6 M HCl to pH 2. The aqueous layer was then extracted with ethyl acetate (3 x 25 mL) and the combined organics washed with brine and dried over NaCl. The organics were then filtered and concentrated *in vacuo* to give 5.23 g of product as a white gum. Yield of 91%.[139]

_N_-Benzoyl pipicolinic acid



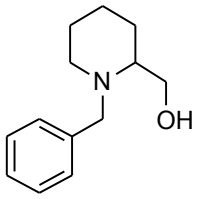
This was prepared as for *N*-benzoyl proline using pipecolinic acid as the starting material. Yield of 4.61 g of product as a white solid. 76% yield.[139]

1-Benzyl-pyrrolidin-2-ylmethanol



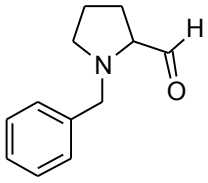
While under argon, a flask containing THF (110 mL) was cooled to 0 ºC. Lithium aluminium hydride (1.79 g, 48 mmol, 2 equiv.) was added in portions to the flask. *N*-benzyl proline dissolved in THF (40 mL) was then added over a period of 15 mins to the solution and the resultant slurry was stirred at 0 ºC for 1h. The mixture was then heated to reflux O/N. The reaction was cooled to 0 ºC and methanol (12 mL) followed by water (5 mL) and 2M NaOH (12 mL) and eventually water again (10 mL) were added. The reaction was then filtered through celite and concentrated *in vacuo* to give 3.95 g of product as an orange oil. Yield of 86%.[140]

(1-Benzyl-pipiridinyl-2-yl)-methanol



This was prepared as for the proline derivative using the pipecolinic acid derivative as the starting material. Yield of 4.87 g of product as an orange oil. Yield 99% Spectroscopic data was in agreement with that previously published.[141]

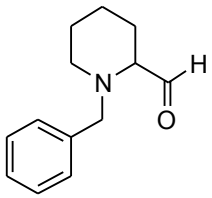
1-Benzyl-pyrrolidine-2-carboxaldehyde



To an argon filled flask DCM (8 mL) and DMSO (0.28 mL, 3.9 mmol, 1.5 equiv.) were added and the reaction was cooled to -40 ºC. Oxalyl chloride (0.35 mL, 3.9 mmol, 1.5 equiv.) was added over 5 mins and the reaction was stirred for 20 mins at -40 ºC. (1-benzyl-pyrrolidin-2-yl)-methanol (0.5 g, 2.6 mmol, 1 equiv.) in DCM (1 mL) was then added to the chilled flask over 5 mins and the reaction was stirred for 15 mins. To this mixture, triethylamine (1.10 mL, 7.9 mmol, 3 equiv.) was added dropwise and the resultant slurry stirred for 30 mins. The reaction mixture was allowed to warm to RT and was washed twice with water. The DCM layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oil was then triturated with ether and any excess triethylamine hydrochloride was filtered off. The ether was then evaporated off and the compound was reacted as crude.

Note: this compound has to be reacted as crude straight away as degradation occurs.

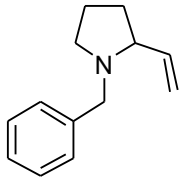
1-Benzyl-pipiridine-2-carbaldehyde



This was prepared as for the proline derivative using the pipecolinic acid derivative as the starting material.

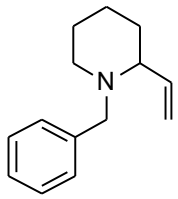
Note: this compound has to be reacted as crude straight away as degradation occurs.

1-Benzyl-2-vinyl-pyrrolidine (115b)



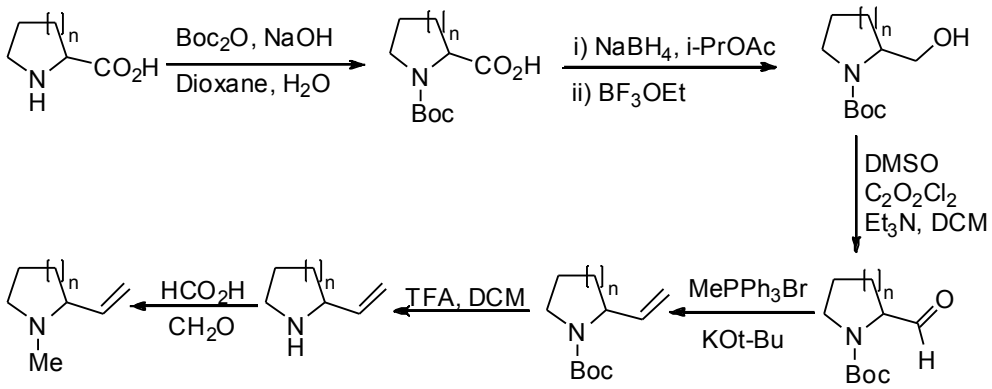
1.6 M n-butyl lithium (1.75 mL, 2.75 mmol, 1.05 equiv.) was added to a solution of methyl-triphenylphosphonium bromide (0.98 g, 2.75 mmoL, 1.05 equiv.) in THF (8 mL) at 0 ºC under a nitrogen atmosphere. The solution was then stirred for 1 h at 0 ºC. This mixture was then added to a solution of 1-benzyl-pyrrolidine-2-carbaldehyde (0.495 g, 2.62 mmol, 1 equiv.) in THF (3 mL). The mixture was stirred at 0 ºC for 30 mins before pouring onto a water/ethyl acetate mix. The aqueous layer was extracted 3 times with ethyl acetate and the combined organic layers washed with brine and dried over sodium sulfate. The reaction was filtered and concentrated *in vacuo* to give crude product. This was then purified using column chromatography (ethyl acetate/hexane 0-25%) to give 277 mg of product as an orange oil in 57% yield over 2 steps. Spectroscopic data was in agreement with that previously published.[142]

1-Benzyl-2-vinyl-pipiridine (115e)

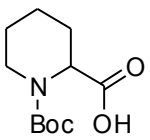


This was prepared as for the proline derivative using the pipecolinic acid derivative as the starting material to give 298 mg of product as an orange oil. 57% yield. Spectroscopic data was in agreement with that previously published.[142]

Synthesis of α-Vinylic Cyclic Amines – Methyl Derivatives



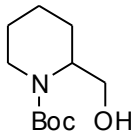
1-*tert*-Butoxycarbonyl-piperidine carboxylic acid



To a solution of pipecolinic acid (10 g, 77 mmol, 1 equiv.), dioxane (150 mL) and water (80 mL), 1 M sodium hydroxide (120 mL) followed by Boc anhydride (40.6 g, 186 mmol, 2.4 equiv.) was added. The reaction was stirred for 48 h before concentration *in vacuo* to a volume of 50 mL. The reaction as then diluted with EtOAc (200 mL) and acidified to pH 2–3 with 5% hydrochloric acid. The solution was extracted 3 times with EtOAc until no amine could be detected by ninhydrin staining on TLC. The combined organics were washed with brine, dried over Na_2SO_4,

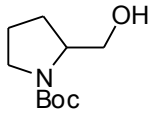
filtered and concentrated *in vacuo*. Product was isolated as an off white solid (17.65 g, 100% yield). Spectroscopic data was in agreement with that previously published.[143]

1-*tert*-Butoxycarbonylpipiridinyl-2-ylmethanol



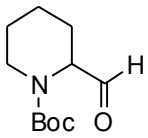
To a mixture of sodium borohydride (2.58 g, 68 mmol, 1.6 equiv.) and isopropylacetate (40 mL) was added *N*-Boc-piperidine carboxylic acid (9.8 g, 43 mmol, 1 equiv.) at -5 to 0 °C in two portions. The reaction was stirred at this temperature for 2 h before adding boron trifluoride etherate (10.8 mL, 86 mmol, 2.1 equiv.) dropwise whilst maintaining the -5 to 0 °C temperature. The resultant slurry was stirred for an additional 3 h at the same temperature before quenching with 0.5 M NaOH. The two phases were separated and the aqueous was extracted 3 times with isopropyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product as a clear oil. 7.15 g, 78% yield. Spectroscopic data was in agreement with that previously published.[144]

1-*tert*-Butoxycarbonyl-pyrrolidin-2-ylmethanol



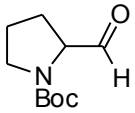
The pyrrolidino derivative was made using the same procedure as for the piperidnyl derivative. From 1-*tert*-butoxyproline (15 g, 70 mmol, 1 equiv.), 14.1 g of product was achieved as a clear oil. 100% yield. Spectroscopic data was in agreement with that previously published.[144]

1-*tert*-Butoxycarbonylpiperidnyl-2-carbaldehyde



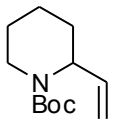
To a solution of freshly distilled oxalyl chloride (2.86 mL, 34 mmol, 1.5 equiv.), in DCM (75 mL) at -78 °C, DMSO (4.8 mL, 68 mmol, 1.1 equiv.) was added. After stirring at -78 °C for 15 mins, 1-*tert*-butoxycarbonylpipiridinyl-2-ylmethanol (4.85 g, 22.5 mmol, 1 equiv.) in DCM (5 mL) was added and the reaction was stirred for a further 15 mins. Triethylamine (12.5 mL, 90 mmol, 4 equiv.) was then added and the reaction was stirred at 0 °C for 1 h. The reaction was then quenched with saturated $NaHCO_3$ solution and the product was extracted three times with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The reaction was then purified *via* column chromatography 0-15% EtOAc in hexane to give product as an orange oil. 3.36 g, 70% yield. Product was reacted immediately to reduce product decomposition.

1-*tert*-Butoxycarbonyl-pyrrolidin-2-ylcarbaldehyde



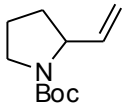
The pyrrolidino derivative was made using the same procedure as for the piperidnyl derivative. From 1-*tert*-butoxycarbonyl-pyrrolidin-2-ylmethanol (14.38 g, 71 mmol, 1 equiv.) to give product as a clear oil. 11.0 g, 77% yield. Product was reacted immediately to reduce product decomposition.

1-*tert*-Butoxycarbonyl-2-vinylpipiridine



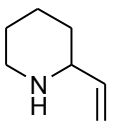
A solution of methyltriphenylphosphonium bromide (8.22 g, 23 mmol, 1.3 equiv.), potassium *tert*-butoxide (2.24 g, 23 mmol, 1.3 equiv.) in THF (200 mL) were heated to reflux for 1 h before allowing to cool to RT. A solution of 1-*tert*-butoxycarbonyl-2-carbaldehyde (3.77 g, 17.7 mmol, 1 equiv.) in THF (50 mL) was then added drop-wise over a period of 1.5 h. The reaction was then stired O/N. The reaction was quenched with water before extracting three times with Et_2O. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude mixture was then purified with column chromatography (0-15% EtOAc in hexane) to give product as a clear oil. 2.86 g, 76% yield. Spectroscopic data was in agreement with that previously published.[144]

1-*tert*-Butoxycarbonyl-2-vinyl-pyrrolidine



The pyrrolidino derivative was made using the same procedure as for the piperidnyl derivative. From 1-*tert*-butoxycarbonyl-pyrrolidin-2-ylcarbaldehyde (11.8 g, 59 mmol, 1 equiv.) to give product as a yellow oil. 10.8 g, 93% yield. Spectroscopic data was in agreement with that previously published.[144]

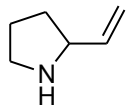
2-Vinylpiperidine (115f)



Trifluoroacetic acid (4.6 mL, 62 mmol, 5 equiv.) was added to a solution of 1-*tert*-butoxycarbonyl-2-vinylpipiridine (2.86 g, 13.5 mmol, 1 equiv.) in DCM (400 mL)

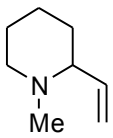
and the reaction was stirred for 1 h. Excess DCM and TFA were evaporated off under reduced pressure. The reaction was taken up in water (50 mL) and was saturated with sodium chloride. The aqueous was then extracted first with Et_2O and then DCM. The combined organics were then dried over Na_2SO_4, filtered and carefully concentrated *in vacuo*. The product was then purified *via* distillation (bpt 143 °C) to give product as a clear oil. 545 mg, 37% yield. Spectroscopic data was in agreement with that previously published.[145]

2-Vinylpyrrolidine (115c')



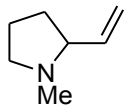
The pyrrolidino derivative was made using the same procedure as for the piperidnyl derivative. From 1-*tert*-butoxycarbonyl-2-vinyl-pyrrolidine (10.79g, 55 mmol, 1 equiv.) 1.89 of product was achieved as a clear oil. 36% yield. This product was used immediately in the next step to prevent degradation.

1-Methyl-2-vinylpiperidine (115d)



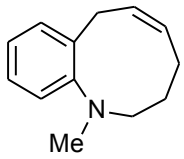
2-vinylpiperidine (400 mg, 3.25 mmol, 1 equiv.), 90 % formic acid (0.34 mL, 8.13 mmol, 2.5 equiv.) and 30% formaldehyde solution (0.43 mL, 4.6 mmol, 1.5 equiv.) were heated together at 50 °C O/N. After cooling to RT, hydrochloric acid (6 N, 0.72 mL) was added. The excess acid was then evaporated off and the residue was carefully treated with 50% NaOH solution (0.36 mL). The mixture was then extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and purified using vacuum distillation (60 °C, 40 mmHg). This yielded product as a clear oil. 76 mg, 17% yield. Spectroscopic data was in agreement with that previously published.[145]

1-Methyl-2-vinylpyrrolidine (115a)



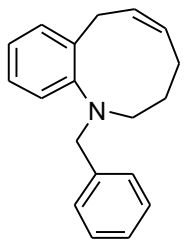
The pyrrolidino derivative was made using the same procedure as for the piperidnyl derivative. From 2-vinyl-pyrrolidine (1.5 g, 15.4 mmol, 1 equiv.) 1.08 g of product was achieved as a clear oil. Boiling point 115 °C, 63% yield. Spectroscopic data was in agreement with that previously published.[146]

(*Z*)-1-Phenyl-2,3,4,7-tetrahydro-1*H*-benzo[*b*]azonine 116a



23.0 mg of product isolated as a colourless oil. 41% yield. ^{1}H NMR, 360 MHz δ_H 7.25-7.15 (3H, m), 7.05-7.00 (1H, m), 5.74 (1H, q, J=8.7), 5.37 (1H, q, J=8.7), 3.53 (2H, br), 2.71 (3H, s), 2.59 (4H, br), 1.56 (2H, br); ^{13}C NMR, 90 MHz δ_C 155.2 (**Q**), 136.8 (**Q**), 130.8 (**C**H), 127.3 (**C**H), 127.3 (**C**H), 126.8 (**C**H), 123.8 (**C**H), 121.0 (**C**H), 57.2 (**C**H_2), 39.5 (**C**H_3), 31.7 (**C**H_2), 25.0 (**C**H_2), 22.8 (**C**H_2); IR (film/cm^{-1}) 2916, 1489, 1454, 1207, 764, 733; HRMS (ESI$^+$) calc for $C_{13}H_{17}NH^+$: $(M + H)^+$ 189.1434. Found: 189.1432.

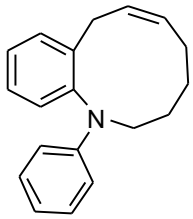
(*Z*)-1-Benzyl-2,3,4,7-tetrahydro-1*H*-benzo[*b*]azonine (116b)



The general procedure was followed to give 15.7 mg of pure product as a clear oil. Yield 30%. ^{1}H NMR, 360 MHz δ_H 7.38-7.34 (2H, m), 7.26-7.08 (6H, m), 6.96 (1H, dt, J=1.3, 7.3), 5.70 (1H, q, J=8.5), 5.35 (1H, q, J=8.5), 4.19 (2H, s), 3.55 (2H, br),

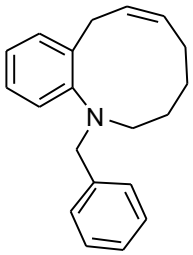
2.84 (2H, t, J=5.7), 2.60 (2H, br), 1.45 (2H, br); ^{13}C NMR, 90 MHz δ_C 152.8 (**Q**), 140.0 (**Q**), 137.5 (**Q**), 130.8 (**C**H), 130.7 (**C**H), 128.7 (**C**H), 128.0 (**C**H), 127.3 (**C**H), 126.6 (**C**H), 124.2 (**C**H), 122.1 (**C**H), 57.1 (**C**H_2), 56.8 (**C**H_2), 31.7 (**C**H_2), 26.0 (**C**H_2), 23.1 (**C**H_2); IR 3006.48, 2915.84, 2813.63, 1487.81, 1453.1, 1131.05, 909.272; HRMS (EI$^+$) calc for $C_{19}H_{21}N$: $(M+H)^+$264.1747. Found: 264.1745.

(*Z*)-1-Phenyl-2,3,4,7-tetrahydro-1*H*-benzo[*b*]azonine (116c)



29.9 mg of product isolated as a colourless oil. 40% yield. ^{1}H NMR, 360 MHz δ_H; 7.32 (1H, m), 7.24-7.14 (4H, m), 6.95 (1H, m), 6.75 (1H, m), 6.6-6.60 (2H, m), 5.72 (1H, q, J=8.9), 5.42 (1H, q, J=8.9), 4.09 (2H, br), 3.74 (2H, br), 3.12 (2H, br), 2.85 (2H, br), 2.43 (1H, br), 1.88 (2H, br), 1.43 (2H, br). ^{13}C NMR, 90 MHz δ_C 150.2 (Q), 149.3 (Q), 140.1 (Q), 130.5 (CH), 130.3 (CH), 129.1 (CH), 128.7 (2CH), 128.2 (CH), 127.7 (CH), 126.8 (CH), 117.4 (CH), 115.1 (2CH), 49.5 (CH_2), 31.1 (CH_2), 25.8 (CH_2), 22.3 (CH_2); IR (film/cm^{-1}) 3008, 2922, 2852, 1599, 1496, 1336, 1279, 750, 692; HRMS (ESI$^+$) calc for $C_{18}H_{19}NH^+$: $(M + H)^+$ 250.1590. Found: 250.1593.

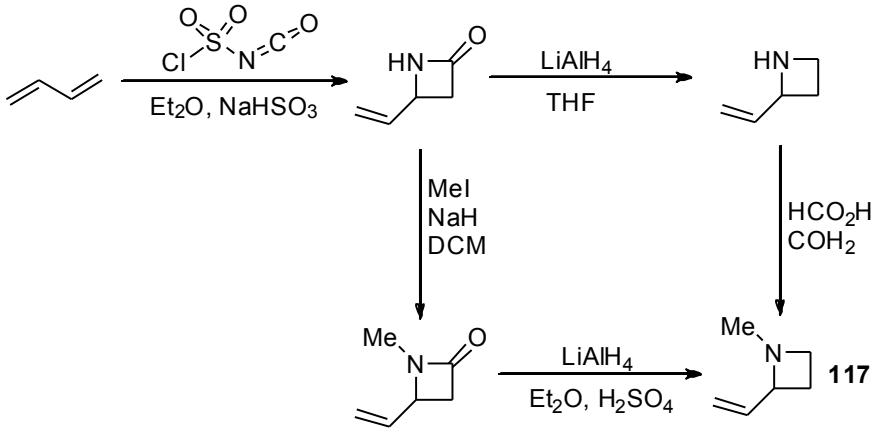
(*Z*)-1-Benzyl-1,2,3,4,5,8-hexahydro-benzo[*β*]azecine (116e)



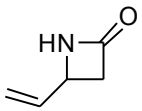
23.3 mg of product isolated as a yellow oil. 28% yield. ^{1}H NMR 360 MHz δ_H; 7.40-7.00 (9H, m), 5.59 (1H, q, J=8.6), 5.17 (1H, q, J=8.6), 3.86 (2H, s), 3.44 (2H, d, J=6.5), 3.01 (2H, t, J=4.8), 2.55 (1H, s), 1.53 (2H, s), 1.41 (2H, td, J=5.8, 11.9), 1.08-

1.00 (2H, m); ^{13}C NMR, 90 MHz δ_C 149.9 (**Q**), 141.3 (**Q**), 138.7 (**Q**), 131.0 (**C**H), 130.0 (**C**H), 129.8 (**C**H), 129.6 (**C**H), 129.6 (**C**H), 129.2 (**C**H), 128.0 (**C**H), 126.9 (**C**H), 126.6 (**C**H), 125.7 (**C**H), 124.9 (**C**H), 64.2 (**C**H_2), 56.9 (**C**H_2), 30.5 (**C**H_2), 29.5 (**C**H_2), 26.0 (**C**H_2), 22.91(**C**H_2); IR (film/cm^{-1}) 2914, 1489, 1452, 731, 700; HRMS (EI$^+$) calc for $C_{20}H_{23}NH^+$: $(M+H)^+$ 278.1906. Found: 278.1908.

Synthesis of α-Vinylic Cyclic Amines-Azetidine Derivatives



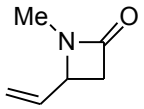
4-Vinyl-2-Azetidinone



Butadiene (13 mL, 148 mmol, 1.5 equiv.) was condensed under nitrogen in a hydrogenation vessel cooled to -20 ºC. Cool ether (50 ml, -20 ºC) and chlorosulfonyl isocyanate (8.73 mL, 100 mmol, 1 equiv.) were then added. The reaction was then stoppered and placed in an ice bath. The ice was allowed to melt and the reaction was allowed to stand for 2 days behind a blast shield. The bottle was then chilled to -78 ºC and opened carefully. The contents were passed to a RB flask covered in dry ice and the bottle was stoppered. The contents were then transferred slowly *via* an insulated cannular to a cooled (-10 ºC) rapidly stirred mixture of 40% sodium bisulfite solution (100 mL) and ether (100 mL). The pH is kept basic by the periodic addition of 1 ml aliquots of NaOH solution (6 M, aq). The layers were then separated and the product was extracted with 3 portions of diethyl ether. The combined organics were then dried over sodium sulfate, filtered and concentrated *in vacuo*. This gave 4.7 g of a yellow

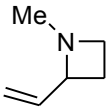
oil which was deemed pure enough to react in the next step. 55% yield. Spectroscopic data was in agreement with that previously published.[147]

1-Methyl-4-vinyl-2-azetidinone



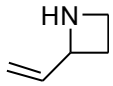
4-vinyl-2-azetidinone (4.28 g, 44 mmol, 1 equiv.), iodomethane (5.5 mL, 88 mmol, 2 equiv.) and sodium hydride (60% in mineral oil, 2.11 g, 88 mmol, 2 equiv.) were added to DCM (200 mL) and the reaction was stirred under N_2 O/N. Further portions of iodomethane (2.75 mL, 44 mmol, 1 equiv.) and sodium hydride (60% in mineral oil, 2.11 g, 88 mmol, 2 equiv.) were then added and the reaction was stirred for a further 48 h. The reaction was then carefully quenched with water and extracted with 3 portions of DCM. The combined organics were then dried over Na_2SO_4, filtered and evaporated to dryness. The crude mixture was then columned using 0-50% EtOAc in hexane. This yielded 2.66 g of product as a yellow oil. 55% yield.[148]

1-Methyl-2-vinylazetidine (117)



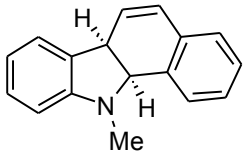
To an ice-cold suspension of lithium aluminium hydride (0.74 g, 19.5 mmol, 1 equiv.) in diethyl ether (100 mL) under nitrogen, 1-methyl-4-vinyl-2-azetidinone (2.16 g, 19.5 mmol, 1 equiv.) was added. The reaction was allowed to warm to RT and was stirred for 2 h. To the resulting mixture, water was added dropwise to quench and the reaction was stirred for 1 h. The solid was removed by filtration and the product was obtained by distillation (180 °C). 1.45 g of product was obtained as a clear oil. Yield 77%.

2-Vinylazetidine



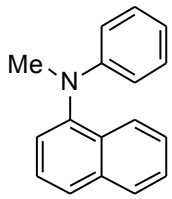
To an ice-cold suspension of lithium aluminium hydride (4.94 g, 130 mmol, 2.7 equiv.) in diethyl ether (160 mL) under nitrogen, sulfuric acid (6.27 g, 1.32 equiv.) was added dropwise. The reaction was stirred for 1 h before adding 4-vinyl-2-azetidinone (4.7 g, 48 mmol, 1 equiv.) and refluxing for 3 days. To the resulting mixture, water (10 mL) was added dropwise and the reaction was stirred for 1 h. The solid was removed by filtration and the product was obtained by careful concentration *in vacuo*. Spectroscopic data was in agreement with that previously published.[149]

11-Methyl-11,11a-dihydro-6a*H*-benzo[*a*]carbazole (121)



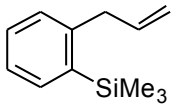
To magnesium turnings (54 mg, 2.3 mmol, 1.1 equiv) in THF (1 mL) was added 1-fluoro-2-bromobenzene (37 μL, 0.17 mmol, 0.17 equiv.). The reaction was then stirred for 10 min before adding *N*-methyl-pyrrole (177 μL, 1 mmol, 1 equiv.) and stirring for a further 40 min. More 1-fluoro-2-bromobenzene (183 μL, 0.83 mmol, 0.83 equiv.) was added with ice-bath cooling and the reaction was stirred at room temperature for 18 h. The reaction was then quenched with sat NH_4Cl solution and extracted three times with diethyl ether. The combined organics were then dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude product was then purified by column chromatography (SiO_2, hexane: DCM 95: 5, dry loading) to afford the product as a white solid (52 mg, 22%). M.p. = 155 ºC (hexane) (lit.[10] = 156-157 ºC); ^{1}H NMR 360 MHz δ_H; 7.40-7.25 (4H, m), 7.23-7.12 (2H, m), 6.84 (1H, dt, J=1.0, 7.4), 6.61 (1H, d, J=7.8), 6.55 (1H, dd, J=2.1, 9.6), 5.70 (1H, ddd, J=0.8, 2.1, 9.6), 4.17-4.08 (2H, m), 2.69 (3H, s); ^{13}C NMR, 90 MHz δ_C 152.43 (**Q**), 132.98 (**Q**), 130.59 (**Q**), 130.44 (**C**H) 130.24 (**Q**), 128.87 (**C**H), 128.77 (**C**H), 127.57 (**C**H), 127.37 (**C**H), 126.83 (**C**H), 125.61 (**C**H), 124.25 (**C**H), 119.22 (**C**H), 67.70 (**C**H), 41.82 (**C**H$_3$), 33.13(**C**H). HRMS (EI) calc for $C_{17}H_{15}N$: 233.11990. Found 233.11992.

Methyl-naphthalen-1-yl-phenyl-amine (123)



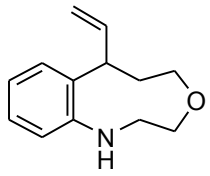
46.2 mg of product isolated as a colourless solid. 66% yield. ^{1}H NMR 360 MHz δ_H; 7.97-7.90 (2H, m), 7.83 (1H, dd, J=0.7, 8.2), 7.57-7.50 (2H, m), 7.47 (1H, tdd, J=1.7, 6.8, 8.7), 7.41 (1H, ddd, J=1.1, 2.0, 7.3), 7.24-7.16 (2H, m), 6.77 (1H, tdt, J=1.0, 2.2, 7.5), 6.67 (2H, ddd, J=1.0, 2.2, 8.9), 3.44 (3H, s); ^{13}C NMR, 90 MHz δ_C 150.07 (**Q**), 145.34 (**Q**), 135.10 (**Q**), 131.30 (**Q**), 128.88 (**C**H), 128.41 (**C**H), 126.60 (**C**H), 126.41 (**C**H), 126.30 (**C**H), 126.18 (**C**H), 125.20 (**C**H), 123.80 (**C**H), 117.18 (**C**H), 113.51 (**C**H), 40.17 (**C**H$_3$). The spectroscopic data was in agreement with that previously published.[150]

(o-allylphenyl)-trimethylsilane (125)



4.0 mg of product isolated as a colourless oil. 7% yield. ^{1}H NMR 360 MHz δ_H; 7.48 (d, 1H, J = 7.2), 7.32 (t, 1H, J = 7.6), 7.22–7.18 (m, 2H), 5.78 (ddt, 1H, J = 6.4, 10.4, 17.2), 5.48 (dd, 1H, J = 2.0, 10.4), 5.31 (dd, 1H, J = 2.0, 17.2), 4.52 (d, 2H, J = 6.4), 0.33 (s, 9H); ^{13}C NMR, 90 MHz δ_C 145.5 (**Q**), 138.4 (**C**H), 137.9 (**C**H), 134.5 (**C**H), 129.2 (**C**H), 129.1 (**C**H), 125.4 (**C**H$_2$), 115.9 (**C**H), 40.1 (**Q**), 0.4 (3**C**H$_3$); LRMS (EI) calc for $C_{12}H_{18}SiH^+$: 191.1. Found 191.1. The spectroscopic data was in agreement with that previously published.[151]

4-oxy-7vinyl-2,3,4,5,6,7-hexahydro-1H-1-benzazonine (126)



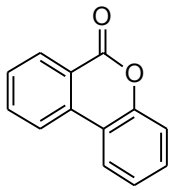
3.6 mg of product isolated as an orange oil. 6% yield. ^{1}H NMR 360 MHz δ_H; 7.24-7.05 (2H, m), 6.72-6.64 (2H, m), 5.90 (1H, ddd, J= 6.0, 9.8, 17.2), 5.14-5.03 (2H, m), 4.24-4.18 (br, m), 3.99-3.84 (2H, m), 3.66-3.60 (2H, m), 3.56-3.42 (2H, m), 2.32-2.24 (2H, m), 2.02-1.94 (2H, m); ^{13}C NMR, 90 MHz δ_C; 148.9 (**Q**), 137.0 (**C**H), 129.2 (**C**H), 116.1 (CH), 114.1 (**C**H_2), 111.4 (**C**H), 109.6 (**Q**), 69.7 (**C**H_2), 67.8 (**C**H_2), 59.2 (**C**H), 47.7 (**C**H_2), 38.5 (**C**H_2); LRMS (EI) calc for $C_{13}H_{17}NO^{+}$: 203.1. Found 203.1.

6.3 Experimental Data for the Generation of Benzyne from Benzoic Acid

General Procedure for Triphenylene Synthesis

Benzoic acid (110 mg, 0.9 mmol, 1 equiv.), palladium(II) acetate (25 mg, 0.11 mmol, 12.5 mol %), 1,10-phenanthroline (21 mg, 0.11 mmol, 12.5 mol %) and sulfolane (25 mL) were placed in an oven dried RB flask. The mixture was heated to around 40 °C to allow sulfolane to become less viscous and the reaction was sonicated until all solids were dissolved. Copper(II) acetate (123 mg, 0.68 mmol, 0.75 equiv.), potassium phosphate dibasic (314 mg, 1.8 mmol, 2 equiv.), tetrabutylammonium bromide (298 mg, 0.9 mmol, 1 equiv.) and 4Å MS (0.4 g) were then added to the mixture. The mixture was then heated to 150 °C for 16 h open to air before allowing to cool. The reaction was then filtered through silica and the silica was washed with ethyl acetate (~150 mL). The resulting solution was then washed with water (4 x 100 mL), once with NaOH solution (1 M, 100 mL) and once with brine (100 mL). The organics were then dried over $MgSO_4$, filtered and evaporated to dryness. The resulting residue was then purified using column chromatography (DCM/hexane 0-5%) to yield triphenylene as a colourless solid (32 mg, 47 % yield).

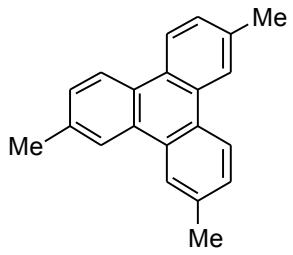
6H-Dibenzo[b,d]pyran-6-one (145b)



Benzoic acid (110 mg, 0.9 mmol, 1 equiv.), palladium(II) acetate (25 mg, 0.11 mmol, 12.5 mol %), *tert*-butyl XPhos (96 mg, 0.11 mmol, 12.5 mol %) and sulfolane (25 mL) were placed in an oven dried RB flask. The mixture was heated to around 40 °C to allow sulfolane to become less viscous and the reaction was sonicated until all solids were dissolved. Copper(II) acetate (328 mg, 1.8 mmol, 2 equiv.), potassium phosphate dibasic (314 mg, 1.8 mmol, 2 equiv.), tetrabutylammonium bromide (298 mg, 0.9 mmol, 1 equiv) and 4Å MS (0.4 g) were then added to the mixture. The mixture was then heated to 150 °C for 16 h, open to air, before allowing to cool. The

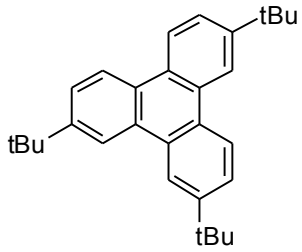
reaction was then filtered through silica and the silica was washed with ethyl acetate (~150 mL). The resulting solution was then washed with water (4 x 100 mL), once with NaOH solution (1M, 100 mL) and once with brine (100 mL). The organics were then dried over $MgSO_4$, filtered and evaporated to dryness. The resulting residue was then purified using column chromatography (EtOAc/hexane 0-6%) to yield 6*H*-Dibenzo[b,d]pyran-6-one (22 mg, 25 % yield) as a colourless solid. ^{1}H NMR 400 MHz δ_H ; 8.42 (1H, dd, J=8.0, 1.0), 8.14 (1H, d, J=8.1), 8.08 (1H, dd, J=7.9, 1.3), 7.84 (1H, ddd, J=8.3, 7.4, 1.3), 7.60 (1H, ddd, J=0.8, 7.4, 8.1), 7.49 (1H, ddd, J=1.5, 7.4, 8.5), 7.38 (1H, dd, J=1.1, 8.4), 7.35 (1H, ddd, J=1.0, 4.8, 8.3). Spectroscopic data was in agreement with that previously published.[152]

2, 6, 11-Trimethyltriphenylene (148a)



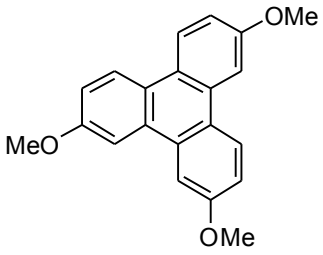
The general procedure was followed except on a 1 mmol scale and yielded 39.4 mg of product as a colourless solid. Yield 34%. ^{1}H NMR 360 MHz δ_H; 8.50 (3H, m), 8.43 (2H, s), 8.39 (1H, s), 7.44 (3H, m), 2.62 (6H, s), 2.61 (3H, s); ^{13}C NMR 90 MHz δ_C; 136.5 (**Q**), 136.2 (**Q**), 136.2 (**Q**), 129.8 (**Q**), 129.5 (**Q**), 129.3 (**Q**), 128.4 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 127.7 (**Q**), 127.5 (**Q**), 127.2 (**Q**), 123.2 (**C**H), 123.2 (2**C**H), 123.0 (**C**H), 123.0 (**C**H), 122.9 (**C**H); mpt 142 °C; HRMS (EI) calc for $C_{21}H_{18}$ 270.1403, found 270.1395.

2, 6, 11-Tri-*tert*-butyltriphenylene (148b)



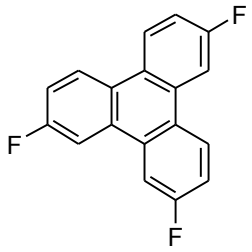
The general procedure was followed yielding 39.4 mg of product as a colourless solid. Yield 33%. ^{1}H NMR 360 MHz δ_H; 8.65 (4H, m), 8.55 (2H, m), 7.71 (3H, m), 1.53 (18H, s), 1.51 (9H, s). ^{13}C NMR 90 MHz δ_C; 149.4 (**Q**), 149.3 (**Q**), 149.2 (**Q**), 129.6 (**Q**), 129.2 (**Q**), 129.0 (**Q**), 127.8 (**Q**), 127.6 (**Q**), 127.2 (**Q**), 124.9 (**C**H), 124.9 (**C**H), 124.7 (2**C**H), 123.0 (**C**H), 122.8 (**C**H), 119.0 (**C**H), 118.9 (**C**H), 118.8 (**C**H), 35.0 (3**Q**), 31.5 (3**C**H_3), 31.4 (6**C**H_3). Spectroscopic data was in agreement with that previously published.[153]

2, 6, 11-Trimethoxytriphenylene (148c)



The general procedure was followed yielding 16.5 mg of product as a yellow solid. Yield 17%. ^{1}H NMR, 360 MHz δ_H; 8.43 (3H, m), 7.92 (3H, m), 7.25 (2H, td, J=2.7, 9.0), 7.19 (1H, dd, J=2.7, 9.0), 4.02 (3H, s), 4.01 (3H, s), 4.00 (3H, s); ^{13}C NMR 90 MHz δ_C; 158.7 (**Q**), 158.2 (**Q**), 158.0 (**Q**), 131.3 (**Q**), 130.2 (**Q**), 129.7 (**Q**), 125.0 (**C**H), 124.4 (**C**H), 124.3 (**Q**), 124.3 (**C**H), 123.8 (**Q**), 122.9 (**Q**), 115.6 (**C**H), 115.4 (**C**H), 114.8 (**C**H), 106.1 (2**C**H), 105.2 (**C**H), 55.5 (2**C**H_3), 55.4 (**C**H_3). Spectroscopic data was in agreement with that previously published.[154]

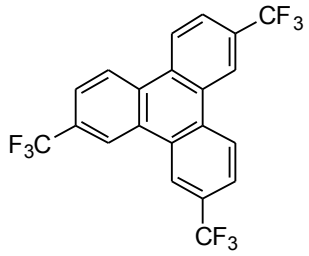
2, 6, 11-Trifluorotriphenylene (148d)



The general procedure was followed yielding 30 mg of product as a colourless solid. Yield 35%. ^{1}H NMR 800 MHz δ_H; 8.47 (2H, dt, J=5.9, 8.6), 8.42 (1H, dd, J=5.6, 8.1), 8.10 (1H, dd, J=2.3, 10.8), 8.04 (2H, m), 7.38 (2H, m), 7.35 (1H, ddd, J=2.3, 7.8, 9.0)

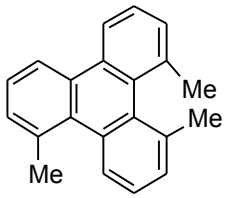
^{13}C NMR, 200 MHz δ_C; 165.1 (**Q**, d, J=248), 164.8 (**Q**, d, J=246), 164.6 (**Q**, d, J=247), 131.4 (**Q**, dd, J=3.0, 8.0), 130.7 (**Q**, d, J=8.0), 130.3 (**Q**, dd, J=2.6, 7.9), 126.2 (**Q**,s), 125.9 (2**Q**, m), 125.9 (**C**H, d, J=8.8), 125.4 (**C**H, dd, J=8.7, 16.2), 116.3 (**C**H, d, J=22.4), 116.2 (**C**H, d, J=22.2), 115.5 (**C**H, dd, 3.1, 22.9), 109.1 (**C**H, dd, J=2.8, 22.8), 109.0 (**C**H, dd, J=2.6, 22.5), 109.0 (**C**H, d, J=7.8), 108.7 (**C**H, d, J=6.8); ^{19}F NMR, 250 MHz δ_F; -112.69, -113.88, -113.93. mpt 230 °C; HRMS (EI) calc for $C_{18}H_9F_3$ 282.0651, found 282.0650.

2, 6, 11-Trifluoromethyltriphenylene (148k)



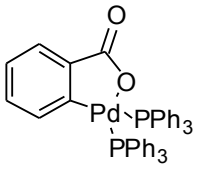
The general procedure was followed, with the exception of the higher temperature of 160 °C, yielding 24.9 mg of product as a yellow solid. Yield 19%. ^{1}H NMR ($(CD_3)_2CO$), 500 MHz δ_H; 9.33 (2H, s), 9.24-9.20 (2H, m), 9.1 (2H, dd, 2.9, 8.7), 8.14-8.09 (3H, m). ^{13}C NMR, 125 MHz δ_C; 134.0 (**Q**), 133.9 (**Q**), 133.6 (**Q**), 132.0 (**Q**, q, J=32.3), 131.9 (**Q**, q, J=32.3), 131.8 (**Q**), 131.5 (**Q**, q, J=33.3), 131.5 (**Q**), 131.4 (**Q**), 127.6 (**C**H), 127.6 (**C**H), 127.3 (**C**H), 126.7 (**C**H, q, J=3.4), 126.4 (**C**H, q, J=3.4), (**C**H, q, J=3.5), 126.4 (**C**F_3, q, J=271.7), 126.3 (**C**F_3, q, J=271.9), 126.3 (**C**F_3, q, J=271.8), 123.5 (3**C**H, m). ^{19}F NMR, 400 MHz δ_F; 114.9 (C**F**$_3$), 114.9 (C**F**$_3$), 114.8 (C**F**$_3$). mpt 280 °C. HRMS (EI) calc for $C_{21}H_9F_9$, 432.0555 found 432.0560.

1,5,12-Trimethyltriphenylene (149a)



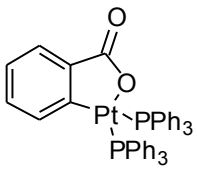
The general procedure was followed yielding 18.7 mg of product as a yellow solid. The fractions from the chromatography column were recrystallised from ether to get pure product. Yield 23%. ^{1}H NMR, 360 MHz δ_H; 8.46 (5H, m), 7.44 (4H, m), 3.04 (3H, s), 2.62 (3H, s), 2.60 (3H, s); ^{13}C NMR 90 MHz δ_C; 136.6 (**Q**), 136.0 (**Q**), 135.0 (**Q**), 131.1 (**C**H), 131.0 (**Q**), 130.9 (**Q**), 130.0 (**Q**), 129.8 (**Q**), 128.6 (**Q**), 128.5 (**C**H), 128.4 (**C**H), 128.1 (**Q**), 126.8 (**C**H), 125.8 (**C**H), 123.6 (**C**H), 123.2 (**C**H), 123.0 (**C**H), 120.8 (**C**H), 26.7 (**C**H_3), 21.8 (**C**H_3), 21.7 (**C**H_3); mpt 100 °C. HRMS (EI) calc for $C_{21}H_{18}$ 270.1403, found 270.1398.

2-oxa-*1*-pallado-3-one-Pd-bis- (triphenylphosphine) (150)



A suspension of 2-iodobenzoic acid (100 mg, 0.4 mmol, 1.5 equiv.), tetrakis (312 mg, 0.27 mmol, 1 equiv.) and toluene (3.5 mL) were heated together at 70 °C O/N. The mixture was filtered off and the solid washed with ether to give palladium insertion product as a yellow solid (232 mg, 98% yield) as product. To this complex was added caesium carbonate (440 mg, 1.35 mmol, 5 equiv) and anhydrous THF (3 mL) and the reaction was stirred O/N. Silver tetrafluoroborate was then added and the reaction was stirred for a further hour. After concentration *in vacuo* DCM was then added and the reaction was filtered through celite. The filtrate was concentrated *in vacuo* and triturated with diethyl ether to give 2-oxa-*1*-pallado-3-one-Pt-bis-(triphenylphosphine) as a yellow solid (49 mg, 25% yield). ^{1}H NMR 400 MHz δ_H 7.81 (6H, dd, J=7.8 ,11.4), 7.60-7.45 (6H, m), 7.40-7.25 (9H, m), 7.15 (3H, dd, J=6.2, 7.6), 7.07 (6H, t, J=6.9), 6.88 (1H, dd, J=1.4, 7.5), 6.62 (1H, t, J=7.2), 6.38 (1H, dt, J=1.7, 7.5), 5.98 (1H, dd, 5.4, 7.2); mpt: product decomposition at 180 °C; IR (film/cm^{-1}) 3049, 1537, 1433, 1096, 739, 690; HRMS (APCI) calc for $C_{43}H_{34}O_2P_2PdH^+$ 747.1163, found 747.1163.

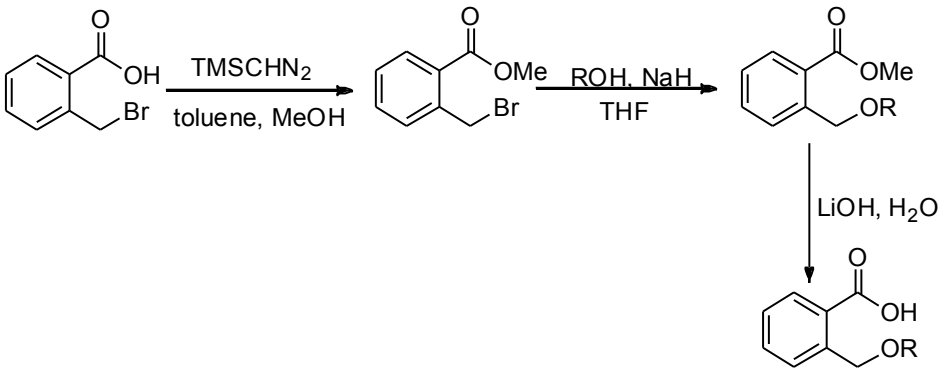
2-oxa-*1*-platinainden-3-one-Pt-bis- (triphenylphosphine) (151)



Platinum tetrakis (386 mg, 3.1 mmol, 1 equiv) was dissolved in degassed dichloroethane (20 mL) and the reaction was warmed to 50 °C. Benzene-2-diazonium-2-carboxylate (50 mg, 3.4 mmol, 1.1 equiv) was added which caused gas evolution and formation of 2-oxa-*1*-platinainden-3-one-Pt-bis- (triphenylphosphine) as a colourless solid. (120 mg, 46% yield). ^{1}H NMR 400 MHz δ_H 7.63 (1H, td, J=2.0, 7.6), 7.53 (6H, ddd, J=1.1, 8.3, 11.8), 7.44 (6H, ddd, J=1.1, 8.3, 11.1), 7.34-7.26 (6H, m), 7.18 (6H, dt, J=2.0, 7.6), 7.12 (6H, dt, J=2.4, 7.9), 6.93 (1H, t, J=7.3), 6.61 (1H, tt, J=1.8, 7.3), 6.38 (1H, t, J=7.3); ^{13}C NMR δ_C (100 MHz); mpt: 157-160 °C. IR (film/cm^{-1}) 3408, 3053, 1643, 1435, 1096, 743, 692, 677. Data was in agreement with that previously published.[155]

Intramolecular Benzyne Reaction Precursors

General Procedure for Compounds **158**, **180a** and **180b**

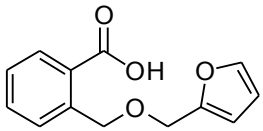


2-bromomethylbenzoic acid (9.27 g, 43 mmol, 1 equiv.), toluene (250 mL) and methanol (170 mL) were placed in a round bottomed flask. Trimethylsilyldiazomethane (2M in ether, 24 mL, 48 mmol, 1.1 equiv.) was added dropwise until a yellow colour persisted. The reaction was then stirred for 1 h before concentrating *in vacuo*. This yielded 9.7 g of 2-bromomethylbenzoic acid methylester as a yellow oil. Material was used without further purification.

Bromomethylbenzoic acid methylester (0.5 g, 2.2 mmol, 1 equiv.), THF (10 mL) and nucleophile (2.6 mmol, 1.2 equiv.) were added to a RB flask. Sodium hydride 60% in mineral oil (176 mg, 2.6 mmol, 1.2 equiv.) was then added portion-wise and the reaction was stirred O/N. The reaction was then quenched with water, extracted with ether and the combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was then reacted without further purification.

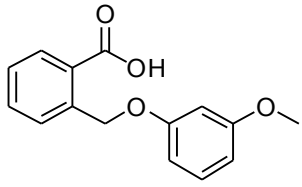
Substituted benzoic acid methylester (2 mmol, 1 equiv.), lithium hydroxide (138 mg, 6 mmol, 3 equiv.), THF (10 mL) and water (10 mL) were heated to 40 °C O/N. Diethyl ether was then added to the reaction and the organic layer was extracted 3 times with 3M NaOH solution. The combined aqueous layers were then acidified with concentrated hydrochloric acid (10 M) before extracting with ether. The combined organics were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was then taken up in a little ether and hexane was added. The ether and some of the hexane was removed resulting in a precipitation of the desired compound from the solution. This precipitate was then filtered off giving pure product.

2-(Furan-2-ylmethoxymethyl)benzoic acid (158)



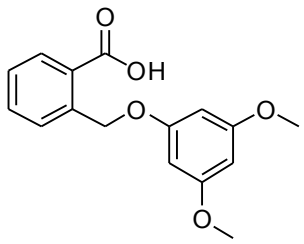
214 mg of product was obtained as a white solid. (42% yield over 3 steps). ^{1}H NMR ($(CD_3)_2CO$), 500 MHz δ_H; 11.28 (1H, br), 7.99 (1H, dd, J=1.3, 7.8), 7.72 (1H, dd, J=0.7, 7.8), 7.59 (1H, dt, J=1.4, 7.7), 7.54 (1H, dd, 0.8, 1.8), 7.39 (1H, ddd, J=0.6, 1.3, 7.9), 6.4 (1H, d, J=2.9), 6.40 (1H, dd, J=1.9, 3.2), 4.95 (2H, s), 4.58 (2H, s) ; ^{13}C NMR 125 MHz δ_C; 169.3 (**Q**), 154.1 (**Q**), 144.7 (**C**H), 142.9 (**Q**), 134.0 (**C**H), 132.4 (**C**H), 130.2 (**Q**), 129.2 (**C**H), 128.7 (**C**H), 112.1 (**C**H), 111.0 (**C**H), 71.4 (**C**H_2), 66.2 (**C**H_2).; mpt 82 °C. IR (film/cm^{-1}) 2891, 1686, 1072, 747; HRMS (EI) calc for $C_{13}H_{13}O_4$ 233.0808, found 233.0810.

2-(3-Methoxyphenoxymethyl) benzoic acid (180a)



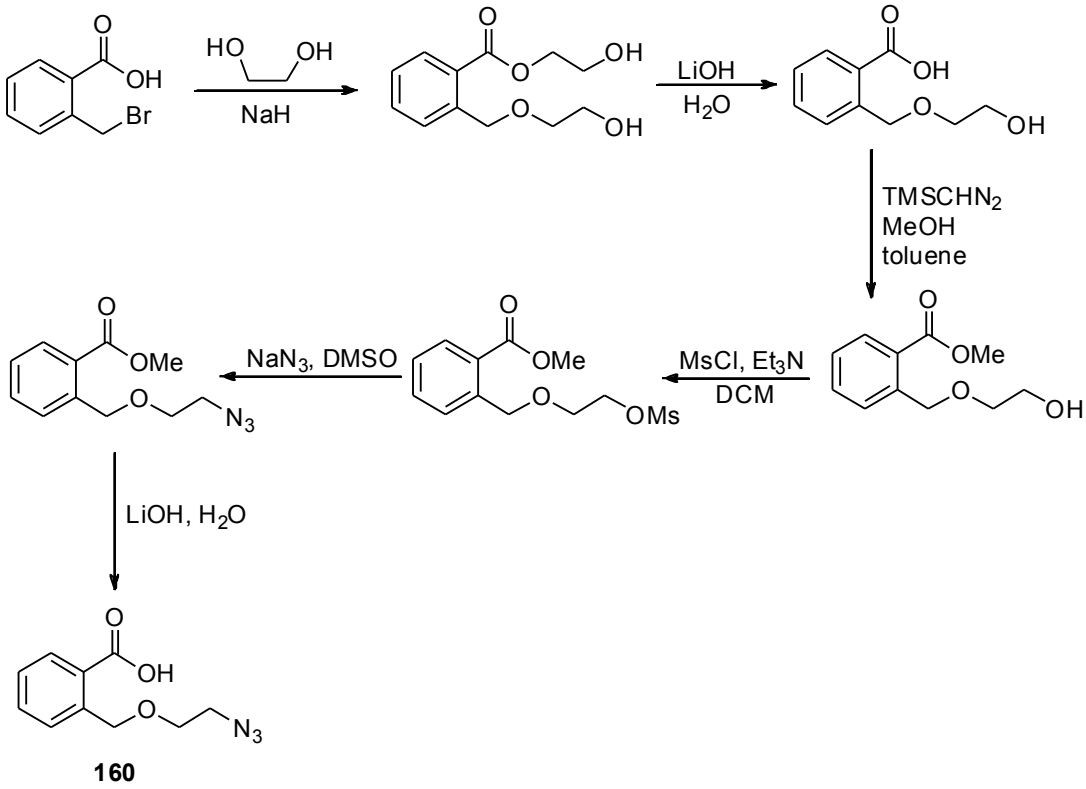
250 mg of product was obtained as an off-white solid. (44% yield over 3 steps). ^{1}H NMR, 500 MHz, δ_H; 11.20 (1H, br), 8.08 (1H, dd, J=1.3, 7.8), 7.76 (1H, dd, J=0.6, 7.8), 7.62 (1H, dt, J=1.3, 7.8), 7.45 (1H, ddd, J=0.6, 1.2, 7.8), 7.18 (1H, m), 6.60-6.52 (3H, m), 5.51 (2H, s), 3.76 (3H, s); ^{13}C NMR 125 MHz δ_C; 169.4 (**Q**), 163.0 (**Q**), 162.0 (**Q**), 141.5 (**Q**), 134.3 (**C**H), 132.7 (**C**H), 131.8 (**C**H), 130.2 (**Q**), 129.4 (**C**H), 129.2 (**C**H), 108.7 (**C**H), 108.3 (**C**H), 103.1 (**C**H), 69.7 (**C**H_2), 56.5 (**C**H_3); mpt 143 °C. IR (film/cm^{-1}) 3017, 2835, 1684, 1491, 1263, 737; HRMS (EI) calc for $C_{15}H_{15}O_4$ 259.0965, found 259.0968.

2-(3-5-Dimethoxyphenoxymethyl) benzoic acid (180b)



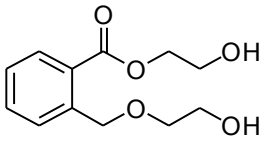
277 mg of product was obtained as an off-white solid. (44% yield over 3 steps). ^{1}H NMR, 500 MHz, δ_H; 11.88 (1H, br), 8.16 (1H, dd, 1.2, 7.8), 7.79 (1H, d, J=7.5), 7.62 (1H, dt, J=1.2, 7.8), 7.42 (1H, t, J=7.5), 6.20 (2H, d, J=2.2), 6.11 (1H, t, J=2.2), 5.52 (2H, s), 3.77 (6H, s); ^{13}C NMR 125 MHz δ_C; 171.9 (**Q**), 161.5 (2**Q**), 160.5 (**Q**), 140.5 (**Q**), 133.6 (**C**H), 131.7 (**C**H), 127.4 (**C**H), 127.4 (**C**H), 126.3 (**Q**), 93.9 (2**C**H), 93.2 (**C**H), 68.2 (**C**H_2), 55.3 (2**C**H_3); mpt 144 °C; IR (film/cm^{-1}) 2942, 1683, 1598, 1151; HRMS (EI) calc for $C_{17}H_{17}O_5$ 289.1071, found 289.1072.

Procedure for Synthesis of Intramolecular Click Reaction Precursor **160**



160

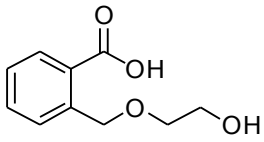
2(2-Hydroxyethoxymethyl)benzoic acid 2-hydroxyethyl ester



60% sodium hydride in mineral oil (0.53 g, 13.2 mmol, 2 equiv.) was added portionwise to a solution of 2-bromomethylbenzoic acid (1.5 g, 6.6 mmol, 1 equiv.) in ethanediol (20 mL) at 0 °C. The reaction was then stirred at RT O/N. The reaction was then quenched with water, before extracting with ether and then DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified using column chromatography 3% Methanol/ DCM to yield 0.81 g of a yellow oil. 51% yield. ^{1}H NMR, 500 MHz, δ_H; 7.94 (1H, dd, J=2.1, 7.7), 7.55-7.45 (2H, m), 7.39 (1H, m), 4.90 (2H, d, J=5.0), 4.48-4.44 (2H, m), 3.95-3.90 (2H, m), 3.75-3.71 (2H, m), 3.59 (2H, dd, J=4.8, 8.9), 3.00 (1H, br), 2.50 (1H, br); ^{13}C NMR δ_C,125 MHz; 168.0 (**Q**), 138.7 (**Q**), 132.1 (**C**H), 130.9 (**C**H),

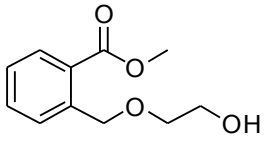
129.5 (**Q**), 129.4 (**C**H), 127.9 (**C**H), 71.8 (**C**H_2), 71.7 (**C**H_2), 66.9 (**C**H_2), 61.8 (**C**H_2), 61.0 (**C**H_2).

2(2-Hydroxyethoxymethyl)benzoic acid



2(2-Hydroxyethoxymethyl)benzoic acid 2-hydroxyethyl ester (0.8 g, 3.3 mmol, 1 equiv.), lithium hydroxide (227 mg, 9.9 mmol, 3 equiv.), water (30 mL) and THF (15 mL) were heated together at 40 °C O/N The reaction was then allowed to cool to RT and ether was added. The ether was then extracted 3 times with 2M NaOH solution. The combined aqueous layers were then acidified with 10M HCl and were then subsequently extracted with ether. The combined organics were then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded 0.65 g of product as a white solid. 100% yield. ^{1}H NMR, 500 MHz, δ_H; 8.05 (1H, dd, J=1.1, 7.8), 7.61 (1H, d, J=7.7), 7.56 (1H, dt, J=1.3, 7.6), 7.39 (1H, dt, 1.2, 7.7), 4.95 (2H, s), 3.86-8.83 (2H, m), 3.75-3.72 (2H, m); ^{13}C NMR 125 MHz δ_C; 171.4 (**Q**), 140.2 (**Q**), 132.9 (**C**H), 131.5 (**C**H), 128.6 (**C**H), 128.0 (**Q**), 127.6 (**C**H), 71.9 (**C**H_2), 71.3 (**C**H_2), 31.7 (**C**H_2); mpt 88 °C.

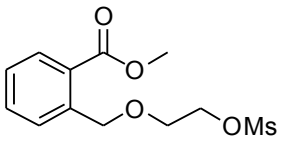
2(2-Hydroxyethoxymethyl)benzoic acid methyl ester



To a solution of 2(2-Hydroxyethoxymethyl)benzoic acid (0.65 g, 3.3 mmol, 1 equiv.), toluene (24 mL) and methanol (15 mL), trimethylsiliyldiazomethane (2M in ether, 1.9 mL, 3.7 mmol, 1.1 equiv.) was added until a yellow colour persisted. The reaction was then allowed to stir for a further hour before concentrating *in vacuo* to give a yellow oil which was used without further purification. ^{1}H NMR, 500 MHz, δ_H; 7.94 (1H, dd, J=1.0, 7.8), 7.61 (1H, d, J=7.7), 7.53 (1H, dt, J=1.2, 7.6), 7.36 (1H, t, J=7.6), 4.93 (2H, s), 3.90 (3H, s), 3.83-3.79 (2H, m), 3.71-3.68 (2H, m), 2.23 (1H, t, J=6.2);

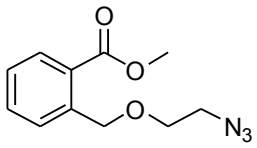
^{13}C NMR 125 MHz δ_C; 171.4 (**Q**), 140.2 (**Q**), 132.9 (**C**H), 131.5 (**C**H), 128.6 (**C**H), 128.0 (**Q**), 127.6 (**C**H), 71.9 (**C**H_2), 71.3 (**C**H_2), 61.7 (**C**H_2), 52.1 (**C**H_3).

2(2-Methanesulfonyloxyethoxymethyl)benzoic acid methyl ester



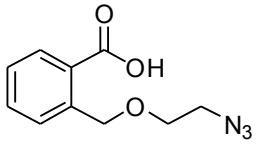
To a solution of (2-Hydroxyethoxymethyl)benzoic acid methyl ester (0.69 g, 3.3 mmol, 1 eq), DCM (17 mL) and triethylamine (0.55 mL, 3.9 mmol, 1.2 equiv.), methanesulfonyl chloride (0.17 mL, 3.9 mmol, 1.2 equiv.) was added dropwise over a period of several minutes. The reaction was then allowed to stir for 15 mins. The mixture was then washed with ice-water, ice cold 10% hydrochloric acid, saturated sodium bicarbonate and saturated brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded 0.7 g of product as an orange oil. 74% yield. ^{1}H NMR, 500 MHz, δ_H; 7.94 (1H, dd, J=0.8, 7.8), 7.63 (1H, d, J=7.3), 7.54 (1H, dt, J=1.0, 7.8), 7.35 (1H, t, J=7.6), 4.97 (2H, s), 4.45-4.42 (2H, m), 3.90 (3H, s), 3.85-3.82 (2H, m), 3.04 (3H, s). ^{13}C NMR 125 MHz δ_C; 167.4 (**Q**), 139.8 (**Q**), 132.4 (**C**H), 130.5 (**C**H), 128.2 (**Q**), 127.7 (**C**H), 127.3 (**C**H), 71.1 (**C**H_2), 69.1 (**C**H_2), 68.5 (**C**H_2), 52.0 (**C**H_3), 37.7 (**C**H_2).

2-(2-Azidoethoxymethyl)benzoic acid methyl ester



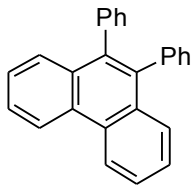
2(2-Methanesulfonyloxyethoxymethyl) benzoic acid methyl ester (0.7 g, 2.4 mmol, 1 equiv.), sodium azide (0.17 g, 2.6 mmol, 1.1 equiv.) and DMSO (10 mL) were heated to 60 °C O/N. The reaction was then quenched with water and extracted three times with EtOAc. The combined organic layers were then washed three times with water, once with brine before drying over $MgSO_4$, filtering and concentration *in vacuo*. The resulting residue was used in the next stage of synthesis without further purification.

2-(2-Azidoethoxymethyl)benzoic acid (160)



2-(2-Azidoethoxymethyl)benzoic acid methyl ester (0.53 g, 2.4 mmol, 1 equiv.), lithium hydroxide (166 mg, 7.2 mmol, 3 equiv.), water (30 mL), and THF (10 mL) were heated together at 40 °C. The reaction was then cooled and 6M NaOH solution (30 mL) and ether (30 mL) were added. The aqueous layer was then collected and the organic layer was washed a further two times with 3M NaOH solution. The combined aqueous layers were then acidified using 10M HCl which resulted in the formation of a white precipitate. This precipitate was filtered off and dried to give 320 mg of product as a white solid. Yield 64%. ^{1}H NMR, 500 MHz, δ_H; 8.11 (1H, dd, J=1.1, 7.8), 7.74 (1H, d, 7.8), 7.62 (1H, dt, J=1.2, 7.7), 7.40 (1H, t, J=7.5), 5.02 (2H, s), 3.80 (2H, t, J=5.0), 3.49 (2H, t, J=5.0). ^{13}C NMR 125 MHz δ_C; 171.6 (**Q**), 141.0 (**Q**),133.5 (**C**H), 131.6 (**C**H),127.6 (**C**H), 127.3 (**C**H), 126.7 (**Q**), 71.2 (**C**H_2), 69.7 (**C**H_2), 50.9 (**C**H_2); mpt 92 °C; IR (film/cm^{-1}) 2860, 2102, 1674, 1273, 729; HRMS (EI) calc for $C_{10}H_{12}O_3N_3$ 222.0873, found 222.0873.

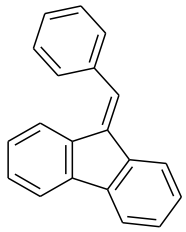
9,10-Diphenylphenanthrene (185)



Benzoic acid (111 mg, 0.9 mmol, 1 equiv), palladium(II) acetate (25 mg, 0.11 mmol, 12.5%), 1,10 phenanthroline (21.3 mg, 0.11 mmol, 12.5%) and sulfolane (25 mL) were placed in an oven dried RB flask. The mixture was heated to around 40 °C to allow sulfolane to become less viscous and the reaction was sonicated until all solids were dissolved. Copper (II) acetate (123 mg, 0.68 mmol, 0.75 equiv), potassium phosphate dibasic (314 mg, 1.8 mmol, 2 equiv), tetrabutylammonium bromide (298 mg, 0.9 mmol, 1 equiv), diphenylacetylene (20 mg, 0.11 mmol, 0.125 equiv) and 4Å

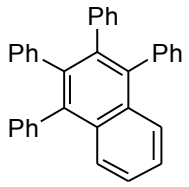
MS (0.4 g) were then added to the mixture. The mixture was then heated to 130 °C for 16 h, open to air, before allowing to cool. The reaction was then filtered through silica and the silica was washed with ethyl acetate (~150 mL). The resulting solution was then washed 4 times with water, once with 1M NaOH solution and once with brine. The organics were then dried over $MgSO_4$, filtered and evaporated to dryness. The resulting residue was then purified using column chromatography (DCM:hexane 0:100 -5:95) to yield 9,10-diphenylphenanthrene (35.5 mg, 48% yield) and triphenylene (38.1 mg, 25% yield, based on benzoic acid) as white solids. ^{1}H NMR 400 MHz δ_H; 8.88 (2H, d, J=8.3), 7.73 (2H, ddd, J=1.4, 6.9, 8.3), 7.64 (2H, dd, J=1.1, 8.3), 7.56 (2H, ddd, J=1.1, 6.9, 8.2), 7.35-7.20 (10H, m). ^{13}C NMR, 100 MHz δ_C; 139.5 (**Q**), 137.2 (**Q**), 131.9 (**Q**), 131.0 (2**C**H), 130.0 (**Q**), 127.8 (**C**H), 127.6 (2**C**H), 126.6 (**C**H), 126.5 (**C**H), 126.4 (**C**H), 122.5 (**C**H). Spectroscopic data was in agreement with that previously published.[156]

9-Benzalflourene (190)



This was formed as a side product in reactions to generate 9,10-diphenylphenanthrene **185** and 1,2,3,4-tetraphenylnaphthalene **191**. Highest yield obtained was a 17% yield of a colourless solid. ^{1}H NMR 400 MHz δ_H; 7.81 (1H, d, J=7.6), 7.76-7.71 (3H, m), 7.64-7.56 (3H, m), 7.48 (2H, t, J=7.4), 7.45-7.30 (4H, m), 7.08 (1H, t, J=7.6); ^{13}C NMR, 100 MHz δ_C; 141.2 (**Q**), 139.4 (**Q**), 139.2 (**Q**), 136.9 (**Q**), 136.5 (**Q**), 136.4 (**Q**), 129.2 (2**C**H), 128.5 (2**C**H), 128.5 (**C**H), 128.2 (**C**H), 128.0 (**C**H), 127.2 (**C**H), 127.0 (**C**H), 126.6 (**C**H), 124.4 (**C**H), 120.2 (**C**H), 119.7 (**C**H), 119.6 (**C**H). Spectroscopic data was in agreement with that previously published.[157]

1,2,3,4-Tetraphenylnaphthalene (191)



Benzoic acid (110 mg, 0.9 mmol, 1 equiv), palladium(II) acetate (25 mg, 0.11 mmol, 12.5%), 1,10 phenanthroline (21 mg, 0.11 mmol, 12.5%) and sulfolane (25 mL) were placed in an oven dried RB flask. The mixture was heated to around 40°C to allow sulfolane to become less viscous and the reaction was sonicated until all solids were dissolved. Copper (II) acetate (123 mg, 0.68 mmol, 0.75 equiv), potassium phosphate dibasic (314 mg, 1.8 mmol, 2 equiv), tetrabutylammonium bromide (298 mg, 0.9 mmol, 1 equiv.), diphenylacetylene (962 mg, 5.4 mmol, 6 equiv) and 4Å MS (0.4 g) were then added to the mixture. The mixture was then heated to 120 °C for 16 h open to air before allowing to cool. The reaction was then filtered through silica and the silica was washed with ethyl acetate (~150 mL). The resulting solution was then washed with water (4 x 100 mL), once with NaOH solution (1M, 100 mL) and once with brine (100 mL). The organics were then dried over $MgSO_4$, filtered and evaporated to dryness. The resulting residue was then purified using column chromatography (DCM:hexane 0:100 – 5:95) to yield 1,2,3,4-tetraphenylnaphthalene (268 mg, 69% yield) as a colourless solid. ^{1}H NMR 400 MHz δ_H; 7.82 (2H, dd, J=3.3, 5.5), 7.56 (2H, dd, J=3.3, 6.5), 7.45-7.33 (10H, m), 7.06-6.96 (10H, m). ^{13}C NMR, 100 MHz δ_C; 140.5 (2**Q**), 139.6 (2**Q**), 138.9 (2**Q**), 138.4 (2**Q**), 132.0 (2**Q**), 131.3 (8**C**H), 127.5 (4**C**H), 127.0 (2**C**H), 126.5 (4**C**H), 126.4 (2**C**H), 125.8 (2**C**H), 125.3 (2**C**H). Spectroscopic data was in agreement with that previously published.[70]

6.4 Experimental Data for the Insertion of Benzyne into Thioesters

General Procedure for Making Thioester Starting Materials

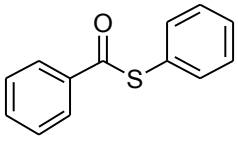
Method A

The thiol (10 mmol, 1 equiv.) and 0.1 M sodium hydroxide solution (100 mL) were cooled to 0 °C and the acid chloride (10 mmol, 1 equiv.) was added dropwise. The reaction was allowed to warm to RT and then stirred O/N. The precipitate was then filtered off washed with water and air dried before recrystallising from hexane.

Method B

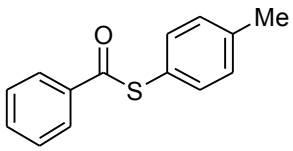
The thiol (10 mmol, 1 equiv.) and 0.1 M sodium hydroxide solution (100 mL) were cooled to 0 °C and the acid chloride (10 mmol, 1 equiv.) was added dropwise. The reaction was allowed to warm to RT and then stirred O/N. Diethyl ether (100 mL) was then added to the reaction and the aqueous layer was extracted 3 times with ether. The combined organics were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was then purified using column chromatography.

Phenylthiobenzoate (200a)



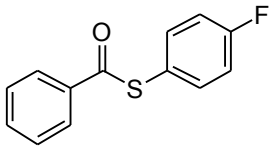
Made using method A. 1.59 g as colourless needles. Yield 74%. ^{1}H NMR 400 MHz δ_H ; 8.06-8.03 (2H, m), 7.62 (1H, tt, J=1.2, 7.4), 7.55-7.45 (7H, m). ^{13}C NMR δ_C (100 MHz); 190.1 (**Q**), 136.6 (**Q**), 135.1 (2**C**H), 133.6 (**C**H), 129.5 (**C**H), 129.2 (2**C**H), 128.7 (2**C**H), 127.5 (2**C**H), 127.3 (**Q**); mpt 55 °C (*lit.* 55-56 °C) Spectroscopic data was in agreement with that previously published.[158]

4-(Methyl)phenylthiol benzoate (200b)



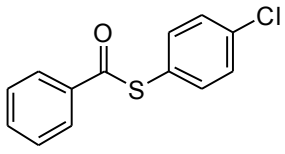
Made using method A. 1.81 g as colourless needles. Yield 79%. ^{1}H NMR δ_H (500 MHz); 8.04-8.01 (2H, m), 7.61 (1H, tt, J=1.2, 7.4), 7.49 (2H, t, J=7.8), 7.40 (2H, d, J=8.1), 7.27 (2H, d, J=7.9), 2.41 (3H, s). ^{13}C NMR δ_C (125 MHz); 190.6 (**Q**), 139.8 (**Q**), 136.7 (**Q**), 135.0 (2**C**H), 133.6 (**C**H), 130.1 (2**C**H), 128.7 (2**C**H), 127.5 (2**C**H), 123.7 (**Q**), 21.4 (**C**H_3); mpt 75-77 °C (*lit.* 76-78 °C). Spectroscopic data was in agreement with that previously published.[158]

4-Fluorophenylthiol benzoate (200c)



Made using method A. To yield 1.11 g of product as colourless needles. Yield 48 %. ^{1}H NMR δ_H (400 MHz); 8.02 (2H, td, J=1.7, 8.6), 7.62 (1H, tt, J=1.2, 7.4), 7.53-7.46 (4H, m), 7.16 (2H, t, J=8.7). ^{13}C NMR δ_C (100 MHz); 190.57 (**Q**, J=12.0), 164.70 (**Q**, J=156), 137.55 (2**C**H, J=8.6), 136.80 (**Q**), 134.19 (**C**H), 129.20 mpt 45 °C (*lit.* 47-49 °C)[159] Spectroscopic data was in agreement with that previously published.[160]

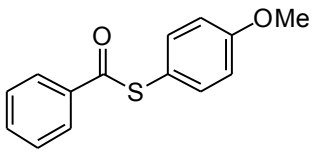
4-Chlorophenylthiol benzoate (200d)



Made using method A. To yield 1.60 g of product as colourless needles. Yield 65 %. ^{1}H NMR δ_H (400 MHz); 8.02 (2H, td, J=1.6, 8.5), 7.63 (1H, tt, J=1.8, 7.4), 7.50 (2H, t, J=7.7), 7.42 (4H, m). ^{13}C NMR δ_C (100 MHz); 189.6 (**Q**), 136.4 (**Q**), 136.3, (2**C**H), 136.0 (**Q**), 133.8 (**C**H), 129.5 (2**C**H), 128.8 (2**C**H), 127.5 (2**C**H), 125.8 (**Q**); mpt

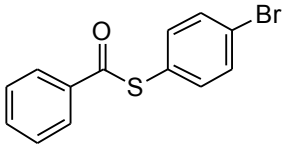
74 °C (*lit.* 76-76.5 °C) Spectroscopic data was in agreement with that previously published.[158]

4-Methoxyphenylthiol benzoate (200e)



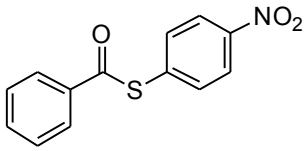
Made using method A. To yield 1.14 g of product as colourless needles. Yield 50 %. ^{1}H NMR δ_H (400 MHz); 8.03 (2H, td, J=1.6, 8.5), 7.60 (1H, tt, J=1.3, 7.4), 7.48 (2H, t, J=7.7), 7.42 (2H, d, J=8.9), 6.99 (2H, d, J=8.9), 3.85 (3H, s). ^{13}C NMR δ_C (100 MHz); 191.0 (**Q**), 160.8 (**Q**), 136.6 (2**C**H), 133.5 (**C**H), 128.7 (2**C**H), 127.4 (2**C**H), 117.9 (**Q**), 115.0 (2**C**H), 55.4 (**C**H_3); mpt 96 °C (*lit.* 100-100.5 °C). Spectroscopic data was in agreement with that previously published.[158]

4-Bromophenylthiol benzoate (200f)



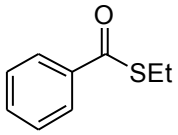
Made using method A. To yield 1.25 g of product as colourless needles. Yield 41 %. ^{1}H NMR δ_H (400 MHz); 8.02 (2H, d, J=1.2, 8.3), 7.63 (1H, m), 7.61-7.57 (2H, m), 7.50 (2H, t, J=7.7), 7.40-7.36 (2H, m); ^{13}C NMR δ_C (100 MHz); 189.5 (**Q**), 136.5 (2**C**H), 136.3 (**Q**), 133.9 (**C**H), 132.4 (2**C**H), 128.8 (2**C**H), 127.5 (2**C**H), 126.5 (**Q**), 124.2 (**Q**). mpt 80-81 °C (*lit.* 78-79 °C).[161] Spectroscopic data was in agreement with that previously published.[160]

4-Nitrophenylthiol benzoate (200g)



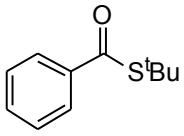
Made using method B. To yield 1.00 g of product as yellow solid. Yield 38 %. ^{1}H NMR δ_H (400 MHz); 8.30 (2H, m), 8.03 (2H, td, J=1.6, 8.5), 7.72 (2H, m), 7.66 (1H, tt, J=1.2, 7.5), 7.53 (2H, t, J=7.8). ^{13}C NMR δ_C (100 MHz); 188.0 (**Q**), 148.3 (**Q**), 136.1 (**Q**), 136.0 (**Q**), 135.4 (2**C**H), 134.3 (**C**H), 129.0 (2**C**H), 127.6 (2**C**H), 123.9 (2**C**H). mpt 112-113 °C (*lit.* 112-113 °C).[161] Spectroscopic data was in agreement with that previously published.[162]

Ethanethiol benzoate (200h)



Made using method B. To yield 1.38 g of product as a waxy colourless solid. Yield 83 %. ^{1}H NMR δ_H (400 MHz); 7.97 (2H, td, J=1.6, 8.5), 7.56 (1H, m), 7.45 (2H, t, J=7.7), 3.08 (2H, q, J=7.4), 1.36 (3H, t, J=7.4), ^{13}C NMR δ_C (100 MHz); 192.1 (**Q**), 137.2 (**Q**), 133.2 (**C**H), 128.5 (2**C**H), 127.1 (2**C**H), 23.4 (**C**H_2), 14.8 (**C**H_3). Spectroscopic data was in agreement with that previously published.[163]

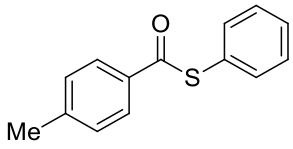
***tert*-Butylthiol benzoate (200i)**



Made using method B. To yield 1.59 g of product as a clear oil. Yield 82 %. ^{1}H NMR δ_H (400 MHz); 7.92 (2H, td, J=1.6, 8.5), 7.53 (1H, m), 7.42 (2H, t, J=7.7), 1.58 (9H, s). ^{13}C NMR δ_C (100 MHz); 192.9 (**Q**), 138.3 (**Q**), 132.9 (**C**H), 128.4 (2**C**H), 126.9

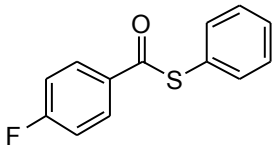
(2**C**H), 48.1 (**Q**), 30.0 (3**C**H_3). Spectroscopic data was in agreement with that previously published.[164]

Phenylthiol 4-methylbenzoate (200j)



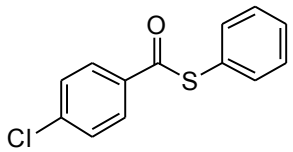
Made using method A. To yield 1.2 g of product as colourless needles. Yield 53%. ^{1}H NMR δ_H (400 MHz);7.94 (2H, d, J=8.3), 7.56-7.50 (2H, m), 7.49-7.43 (3H, m), 7.29 (2H, d, J=7.9), 2.44 (3H, s); ^{13}C NMR δ_C (100 MHz);189.7 (**Q**), 144.6 (**Q**), 135.1 (2**C**H), 134.1 (**Q**), 129.4 (2**C**H), 129.4 (**C**H), 129.2 (2**C**H), 128.0 (**Q**), 127.5 (2**C**H), 21.7 (**C**H_3). mpt 80 °C (*lit.* 76-77 °C).[161] Spectroscopic data was in agreement with that previously published.[158]

Phenylthiol 4-fluorobenzoate (200k)



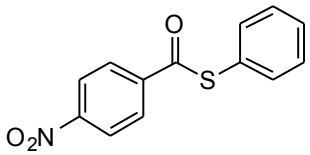
Made using method A. To yield 0.86 g of product as colourless needles. 37% yield. ^{1}H NMR δ_H (400 MHz); 8.10-8.04 (2H, m), 7.55-7.50 (3H, m), 7.49-7.45 (2H, m), 7.17 (2H, t, J=8.6); ^{13}C NMR δ_C; 188.6 (**Q**), 166.0 (**Q**, d, J=255), 135.1 (2**C**H), 132.9 (**Q**, J=3.0), 130.1 (2**C**H, d, J=9.4), 129.6 (**C**H), 129.3 (2**C**H), 127.0 (**Q**), 116.0 (2**C**H, d, J=22); Mpt 58 °C (*lit.* 58-59 °C) Analytical data was in agreement with that previously published.[165]

Phenylthiol 4-chlorobenzoate (200l)



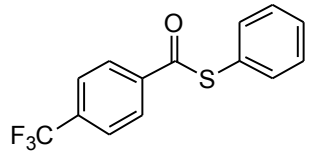
Made using method A. To yield 2 g of product as white needles. Yield 81 %. ^{1}H NMR δ_H (400 MHz); 7.99-7.95 (2H, m), 7.54-7.42 (7H, m). ^{13}C NMR δ_C (100 MHz); 189.1 (**Q**), 140.1 (**Q**), 135.1 (2**C**H), 135.0 (**Q**), 129.7 (**Q**), 129.3 (2**C**H), 129.1 (2**C**H), 128.8 (2**C**H), 126.9 (**Q**). mpt 72 °C (*lit.* 71-72 °C).[166] Spectroscopic data was in agreement with that previously published.[158]

Phenylthiol 4-nitrobenzoate (200m)



Made using method B. To yield 0.83 g of product as a yellow solid. Yield 32%. ^{1}H NMR δ_H (400 MHz); 8.36-8.34 (2H, m), 8.20-8.16 (2H, m), 7.55-7.45 (5H, m); ^{13}C NMR δ_C (100 MHz); 188.8 (**Q**), 150.6 (**Q**), 141.3 (**Q**), 134.9 (2**C**H), 130.1 (**C**H), 129.5 (2**C**H), 128.5 (2**C**H), 126.1 (**Q**), 124.0 (2**C**H). mpt 142 °C (*lit.* 145-147 °C) Spectroscopic data was in agreement with that previously published.[167]

Phenylthiol 4-trifluoromethylbenzoate (200n)

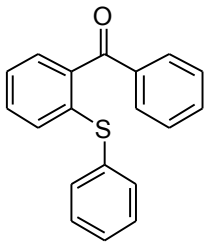


Made using method A. To yield 1.76 g of product as colourless needles. Yield 62 %. NMR δ_H (400 MHz); 8.14 (2H, d, J=8.2), 7.76 (2H, d, J=8.2), 7.55-7.45 (5H, m); ^{13}C NMR δ_C (100 MHz); ^{13}C NMR δ_C (100 MHz); 189.4 (**Q**), 139.4 (**Q**), 135.0 (2**C**H), 134.9 (**Q**, q, J=33), 129.9 (**C**H), 129.4 (2**C**H), 127.8 (2**C**H), 126.6 (**Q**), 125.8 (2**C**H, q, J=3.7), 123.5 (**Q**, q, J=276). mpt 113 °C (*lit.* 114-115 °C)[168] Spectroscopic data was in agreement with that previously published.[160]

General Method for Benzyne Insertion into Thioesters

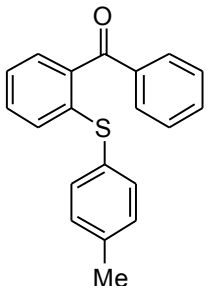
To a mixture of thioester (0.25 mmol, 1 equiv.), TBAT (405 mg, 0.75 mmol, 3 equiv.), bis(dibenzylideneacetone)palladium (4.2 mg, 7.5 μmol, 0.03 mol %), 1,2-bis(diphenylphosphino)ethane (3.6 mg, 8.8 μmol, 0.035 mol %) and toluene (3 mL), was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (101 μL, 0.375 mmol, 1.5 equiv.). The reaction was heated to 120 ºC O/N before allowing to cool to RT. The solvent was then removed *in vacuo* and the resulting residue purified by column chromatography (EtOAc/hexane 1.5%) to give pure product.

Phenyl-(2-phenylsulfanylphenyl)methanone (201a)



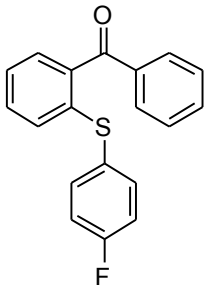
The general procedure was followed to yield 45.2 mg of product as a yellow oil. Yield 62%. NMR δ_H (400 MHz); 7.81 (2H, td, J=1.6, 8.4), 7.64 (1H, ddd, J=1.6, 2.8, 3.6), 7.58 (1H, m), 7.48-7.22 (10H, m); ^{13}C NMR δ_C (100 MHz); 196.5 (**Q**), 139.2 (**Q**), 137.4 (**Q**), 137.2 (**Q**), 134.7 (**Q**), 133.1 (**C**H), 132.8 (2**C**H), 131.4 (**C**H), 130.9 (**C**H), 130.2 (2**C**H), 129.7 (**C**H), 129.3 (2**C**H), 128.4 (2**C**H), 127.9 (**C**H), 125.9 (**C**H); IR (film/cm^{-1}) 3059, 1667, 1286, 699; HRMS (APCI) calc for $C_{19}H_{15}OS^+$ 291.0838, found 291.0834.

Phenyl(2-*p*-tolylsulfanyl-phenyl)methanone (201b)



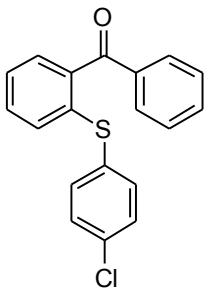
The general procedure was followed to yield 45.0 mg of product as a yellow oil. Yield 59%. ^{1}H NMR δ_H (500 MHz); 7.81 (2H, dd, J=1.1, 8.2), 7.58 (1H, t, J=7.4), 7.46 (2H, t, J=7.7), 7.42 (1H, dd, J=1.3, 7.6), 7.34-7.29 (3H, m), 7.22 (1H, dt, J=1.1, 7.4), 7.16 (1H, dd, J=0.7, 8.0), 7.13 (2H, d, J=8.0), 2.34 (3H, s); ^{13}C NMR δ_C (125 MHz); 196.5 (**Q**), 138.7 (**Q**), 138.3 (**Q**), 138.2 (**Q**), 137.4 (**Q**), 133.7 (2**C**H), 133.0 (**C**H), 130.9 (**C**H), 130.4 (**Q**), 130.3 (**C**H), 130.2 (4**C**H), 129.7 (**C**H), 128.4 (2**C**H), 125.2 (**C**H). 21.2 (**C**H$_3$); IR (film/cm^{-1}) 2924, 1668, 1286; HRMS (APCI) calc for $C_{20}H_{17}OS^+$ 305.0995, found 305.0993.

[2-(4-Fluoro-phenylsulfanyl)-phenyl]-phenyl-methanone (201c)



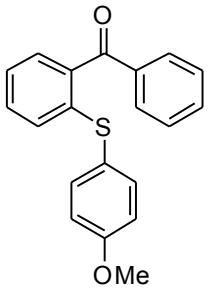
The general procedure was followed to yield 37.5 mg of product as a yellow oil. Yield 49%. NMR ^{1}H NMR δ_H (400 MHz); 7.80 (2H, td, J=1.6, 8.4), 7.59 (1H, m), 7.50-7.43 (3H, m), 7.40-7.33 (3H, m), 7.25 (1H, dt, J=1.1, 7.5), 7.16 (1H, dd, J=0.8, 8.0), 7.04-6.98 (2H, m); ^{13}C NMR δ_C (100 MHz); 196.4 (**Q**), 162.8 (**Q**, d, J=249), 138.4 (**Q**), 138.0 (**Q**), 137.3 (**Q**), 135.5 (2**C**H, J=8.4), 131.1 (**C**H), 131.0 (**C**H), 130.6 (**C**H), 130.1 (2**C**H), 129.9 (**C**H), 129.4 (**Q**, d, J=3.4), 128.4 (2**C**H), 125.7 (**C**H), 116.5 (2**C**H, d, J=21.9). IR (film/cm^{-1}) 3062, 2925, 1667, 1489, 1286, 1225, 700; HRMS (APCI) calc for $C_{19}H_{14}FOS^+$ 309.0744, found 309.0739.

[2-(4-Chloro-phenylsulfanyl)-phenyl]-phenyl-methanone (201d)



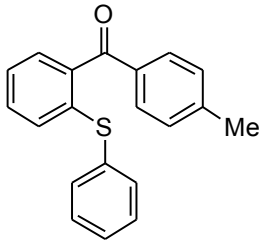
The general procedure was followed to yield 35.4 mg of product as a yellow oil. Yield 43%. NMR ^{1}H NMR δ_H (400 MHz); 7.82 (2H, td, J=1.5, 8.4), 7.62 (1H, m), 7.51-7.45 (3H, m), 7.41 (1H, dt, J=1.6, 7.6); ^{13}C NMR δ_C (100 MHz); 196.3 (**Q**), 139.6 (**Q**), 137.2 (**Q**), 136.3 (**Q**), 133.9 (**Q**), 133.7 (2**C**H), 133.4 (**Q**), 133.2 (**C**H), 131.7 (**C**H), 131.0 (**C**H), 130.1 (2**C**H), 129.7 (**C**H), 129.4 (2**C**H), 128.4 (2**C**H), 126.3 (**C**H). IR (film/cm^{-1}) 3060, 2359, 1668, 1475, 1285; HRMS (APCI) calc for $C_{19}H_{13}ClOSH^{+}$ 325.0448, found 325.0443.

[2(4-Methoxyphenylsulfanyl)phenyl]phenylmethanone (201e)



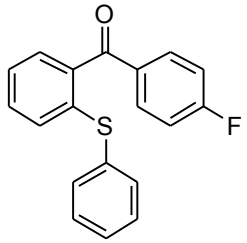
The general procedure was followed to yield 20 mg of product as a yellow oil. Yield 25%. ^{1}H NMR δ_H (400 MHz); 7.82 (2H, dd, J=1.2, 8.2), 7.62-7.55 (1H, m), 7.47 (2H, t, J=7.6), 7.43-7.36 (3H, m), 7.30 (1H, m), 7.19 (1H, dd, J=1.1, 7.4), 7.07 (1H, dd, J=0.6, 8.1), 6.90-6.85 (2H, m); ^{13}C NMR δ_C (100 MHz); 196.5 (**Q**), 160.1 (**Q**), 140.1 (**Q**), 137.5 (**Q**), 136.2 (2**C**H), 135.5 (**Q**), 133.0 (**C**H), 130.9 (**C**H), 130.2 (2**C**H), 129.9 (**C**H), 129.2 (**C**H), 128.4 (2**C**H), 124.7(**C**H), 123.9 (**Q**), 115.0 (2**C**H), 55.3 (**C**H$_3$); IR (film/cm^{-1}) 2926, 1653, 1494, 1247; HRMS (APCI) calc for $C_{20}H_{17}O_2S^{+}$ 321.0944, found 321.0944.

(2-Phenylsulfanylphenyl)-*p*-tolylmethanone (201j)



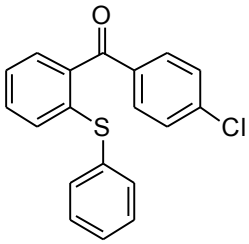
The general procedure was followed to yield 40.3 mg of product as a yellow oil. Yield 53%. NMR ^{1}H NMR δ_H (400 MHz); 7.73-7.69 (2H, m), 7.41 (1H, dd, J=1.4, 7.5), 7.37-7.22 (10H, m), 2.43 (3H, s); ^{13}C NMR δ_C (100 MHz); 196.1 (**Q**), 144.1 (**Q**), 139.8 (**Q**), 136.7 (**Q**), 134.8 (**Q**), 134.7 (**Q**), 132.6 (2**C**H), 131.4 (**C**H), 130.7 (**C**H), 130.3 (2**C**H), 129.3 (**C**H), 129.2 (2**C**H), 129.1 (2**C**H), 127.7 (**C**H), 126.0 (**C**H), 21.7 (**C**H$_3$). IR (film/cm^{-1}) 2924, 1661, 1604, 1286, 743; HRMS (APCI) calc for $C_{20}H_{17}OS^{+}$ 305.0995, found 305.0990.

(4-Fluorophenyl)(2-phenylsulfanylphenyl)methanone (201k)



The general procedure was followed to yield 32.3 mg of product as a yellow oil. Yield 42%. NMR ^{1}H NMR δ_H (400 MHz); 7.83-7.88 (2H, m), 7.45-7.28 (9H, m), 7.14 (2H, t, J=8.7); ^{13}C NMR δ_C (100 MHz); 194.9 (**Q**), 165.8 (**Q**, d, J=255), 139.2 (**Q**), 136.7 (**Q**), 134.5 (**Q**), 133.7 (**Q**, d, J=3.0), 132.7 (2**C**H, d, J=9.4), 132.5 (2**C**H+**C**H), 131.6 (**C**H), 130.9 (**C**H), 129.3 (2**C**H), 127.8 (**C**H), 126.1 (**C**H), 115.6 (2**C**H, d, J=22.0); IR (film/cm^{-1}) 2925, 1668, 1598, 748; HRMS (APCI) calc for $C_{19}H_{14}FOS^{+}$ 309.0744, found 309.0743.

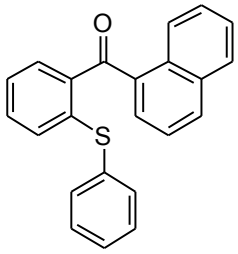
(4-Chlorophenyl)(2-phenylsulfanylphenyl)methanone (201l)



The general procedure was followed to yield 28 mg of product as a yellow oil. Yield 34%. NMR ^{1}H NMR δ_H (400 MHz); 7.75-7.71 (2H, m), 7.43-7.39 (3H, m), 7.39-7.24 (8H, m); ^{13}C NMR δ_C (100 MHz); 195.2 (**Q**), 139.6 (**Q**), 138.9 (**Q**), 137.0 (**Q**), 135.7 (**Q**), 134.4 (**Q**), 132.6 (2**C**H), 131.6 (**C**H), 131.4 (2**C**H), 131.1 (**C**H), 129.4 (**C**H),

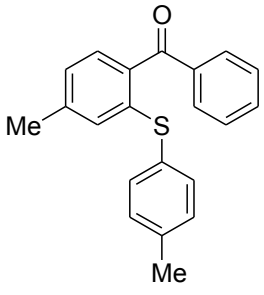
129.3 (2**C**H), 128.7 (2**C**H), 127.9 (**C**H), 126.1 (**C**H); IR (film/cm^{-1}) 2925, 1667, 1585, 928, 745; HRMS (APCI) calc for $C_{19}H_{13}ClOSH^+$ 325.0448, found 325.0448.

Naphthalen-1-yl-(2-phenylsulfanyl-phenyl)-methanone (201m)

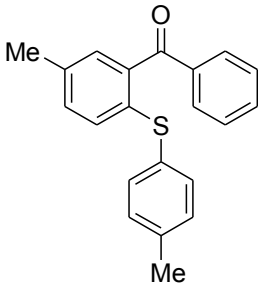


The general procedure was followed to yield 19.6 mg of product as a yellow oil. Yield 23%. NMR ^1H NMR δ_H (500 MHz); 8.43 (1H, m), 8.00 (1H, d, J=8.2), 7.92 (1H, m), 7.60-7.52 (3H, m), 7.50-7.44 (4H, m), 7.39-7.34 (3H, m), 7.32 (1H, ddd, J=1.5, 7.6, 8.1), 7.14 (1H, dt, J=1.1, 7.6), 7.11 (1H, dd, J=0.6, 8.0); ^{13}C NMR δ_C (125 MHz); 198.2 (**Q**), 140.6 (**Q**), 138.0 (**Q**), 136.0 (**Q**), (2**C**H), 133.8 (**Q**), 133.8 (**Q**), 132.2 (**C**H), 132.0 (**C**H), 131.8 (**C**H), 131.0 (**Q**), 129.7 (**C**H), 129.5 (**C**H), 129.5 (2**C**H), 128.4 (**C**H), 128.4 (**C**H), 127.7 (**C**H), 126.5 (**C**H), 125.9 (**C**H), 125.0 (**C**H), 124.3 (**C**H); IR (film/cm^{-1}) 2925, 1654, 1245, 744; HRMS (APCI) calc for $C_{23}H_{16}OSH^+$ 341.0995, found 341.0993.

(4-Methyl-2-*p*-tolylsulfanyl-phenyl)-phenyl-methanone (203a) &
(3-Methyl-2-*p*-tolylsulfanyl-phenyl)-phenyl-methanone (203a')



203a



203a'

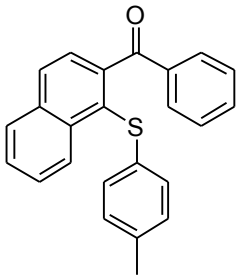
The general procedure was followed to yield 27.8 mg of product as a yellow oil. Yield 35% isolated as a mixture of two regioisomers in a ratio of 48:52 A:B.

Regioisomer A: ^{1}H NMR δ_H (500 MHz); 7.81-7.78 (2H, m), 7.57 (1H, m), 7.47-7.42 (2H, m), 7.23-7.20 (3H, m), 7.16-7.15 (2H, m), 7.08 (2H, d, J=7.9), 2.34 (3H, s), 2.31 (3H, s); ^{13}C NMR δ_C (125 MHz); 196.7 (**Q**), 148.6 (**Q**), 139.6 (**Q**), 137.6 (**Q**), 137.4 (**Q**), 133.6 (**Q**), 133.0 (**C**H), 132.5 (2**C**H), 131.7 (**C**H), 131.6 (**C**H), 130.1 (2**C**H), 129.9 (2**C**H), 129.8 (**C**H), 128.3 (2**C**H), 122.0 (**Q**), 21.1(**C**H_3), 20.9 (**C**H_3);

Regioisomer B: ^{1}H NMR δ_H (500 MHz); 7.81-7.78 (2H, m), 7.57 (1H, m), 7.47-7.42 (2H, m), 7.34 (1H, dd, J=7.8), 7.30 (2H, td, J=1.8, 8.2), 7.13 (2H, d, J=7.9), 7.02 (1H, ddd, J=0.6, 1.4, 7.8), 6.97 (1H, s); 2.35 (3H, s), 2.27 (3H, s); ^{13}C NMR δ_C (125 MHz); 196.4 (**Q**), 141.5 (**Q**), 138.9 (**Q**), 138.2 (**Q**), 137.8 (**Q**), 136.1 (**Q**), 135.3 (**Q**), 133.5 (2**C**H), 132.7 (**C**H), 130.7 (**C**H), 130.1 (2**C**H), 130.1 (2**C**H), 128.3 (2**C**H), 126.1 (**C**H), 21.5 (**C**H_3), 21.1 (**C**H_3);

IR (film/cm^{-1}) 2921, 1667, 703; HRMS (APCI) calc for $C_{21}H_{18}OS^{+}$ 319.1151, found 319.1151.

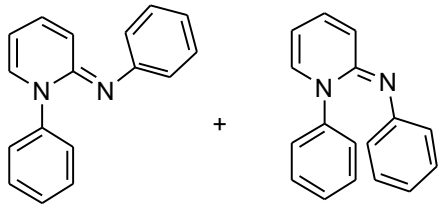
Phenyl-(1-*p*-tolylsulfanyl-naphthalen-2-yl)-methanone (203b)



The general procedure was followed to yield 9.7 mg of product as an orange oil. Yield 11%. NMR ^{1}H NMR δ_H (500 MHz); 7.87-7.83 (3H, m), 7.80 (1H, d, J=8.7), 7.58 (1H, m), 7.55 (1H, dd, J=0.5, 8.4), 7.48 (1H, ddd, J=1.2, 6.9, 8.1), 7.46-7.40 (3H, m), 7.37 (1H, d, J=8.7), 7.21-7.18 (2H, m), 7.06 (2H, d, J=8.0), 2.30 (3H, s); ^{13}C NMR δ_C (125 MHz); 197.8 (**Q**), 138.9 (**Q**), 137.6 (**Q**), 137.5 (**Q**), 133.8 (**C**H), 132.1 (**Q**), 131.7 (2**C**H), 131.5 (**Q**), 131.0 (**Q**), 130.9 (**Q**), 129.9 (2**C**H), 129.7 (2**C**H), 129.7 (**C**H), 129.0 (**C**H), 128.8 (2**C**H), 128.2 (**C**H), 127.4 (**C**H), 126.6 (**C**H), 125.1 (**C**H), 21.1 (**C**H_3); IR (film/cm^{-1}) 2924, 1668, 1238, 810, 712; HRMS (APCI) calc for $C_{24}H_{18}OSH^{+}$ 355.1151, found 355.1147.

6.5 Experimental Data for Ene Reaction

Phenyl-1H-pyridin(2*E*)ylidene]amine (211a) &
Phenyl-1H-pyridin(2*Z*)ylidene]amine (211b)



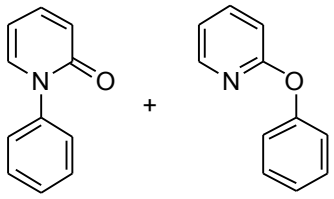
211a **211b**

2-anilinopyridine (191 mg, 1.13 mmol, 3 equiv.), caesium fluoride (200 mg, 1.13 mmol, 3 equiv.) and acetonitrile (2 mL) were placed in a round bottomed flask and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (101 μL, 0.375 mmol, 1 equiv.) was added. The reaction was then stirred at room temperature O/N. The reaction was then filtered and concentrated *in vacuo* before purifying using column chromatography (hexane/EtOAc 0-80%) to yield 67.2 mg of Phenyl[1-phenyl-1*H*-pyridin(2*E*)ylidene]amine as a yellow solid and 17 mg of Phenyl[1-phenyl-1*H*-pyridin(2*Z*)ylidene]amine as a brown solid (91% yield with a 4:1 ratio of *E*:*Z*).

221a: ^{1}H NMR δ_H (400 MHz); 7.50-7.44 (4H, m), 7.35 (1H, m), 7.24 (2H, dd, J=7.6, 8.2), 7.06 (1H, ddd, J=0.7, 1.8, 7.0), 6.92 (1H, tt, J=1.1, 7.6), 6.87-6.79 (3H, m), 6.44 (1H, d, J=9.4), 5.81 (1H, ddd, J=1.3, 6.4, 7.1); ^{13}C NMR δ_C (100 MHz); 153.0 (**Q**), 151.1 (**Q**), 142.9 (**Q**), 138.4 (**C**H), 135.1 (**C**H), 129.3 (2**C**H), 129.2 (2**C**H), 127.8 (**C**H), 127.1 (2**C**H), 122.3 (2**C**H), 121.5 (**C**H), 115.6 (**C**H), 102.8 (**C**H). Mpt 113 °C (*lit.* 114-116 °C) Analytical data was in agreement with that previously published.[169]

211b: ^{1}H NMR δ_H (400 MHz); 7.50-7.44 (4H, m), 7.37 (1H, ddt, J=3.0, 4.2, 5.2), 7.26-7.22 (2H, m), 7.09 (1H, ddd, J=0.6, 1.7, 7.0), 6.92 (1H, tt, J=1.1, 7.4), 6.89 (1H, ddd, J=1.9, 6.4, 9.6), 6.82 (2H, m), 6.46 (1H, d, J=9.6), 5.86 (1H, ddd, J=1.3, 6.4, 7.1); ^{13}C NMR δ_C (100 MHz); 153.0 (**Q**), 150.5 (**Q**), 142.7 (**Q**), 138.6 (**C**H), 135.5 (**C**H), 129.5 (2**C**H), 129.3 (2**C**H), 128.1 (**C**H), 127.1 (2**C**H), 122.5 (2**C**H), 121.8 (**C**H), 115.6 (**C**H), 103.3 (**C**H).

1-Phenyl-1*H*-pyridin-2-one (214) & 2-Phenoxypyridine (215)



214 **215**

The general procedure was followed to yield 24 mg of 1-Phenyl-1*H*-pyridin-2-one as a clear oil (37 % yield) and 23 mg of 2-Phenoxypyridine as a clear oil (35% yield).

1-Phenyl-1*H*-pyridin-2-one (**204)**: ^{1}H NMR δ_H (400 MHz); 7.52-7.44 (2H, m), 7.45-7.36 (4H, m), 7.33 (1H, ddd, J=0.6, 2.1, 6.9), 6.66 (1H, d, J=9.2), 6.23 (1H, dt, J=1.3, 6.7); ^{13}C NMR δ_C (100 MHz); 162.4 (**Q**), 140.9 (**Q**), 139.8 (**C**H), 137.9 (**C**H), 129.3 (2**C**H), 128.4 (**C**H), 126.5 (2**C**H), 121.9 (**C**H), 105.8 (**C**H). Spectroscopic data was in agreement with that previously published.[170]

2-Phenoxypyridine (**205)**: ^{1}H NMR δ_H (400 MHz); 8.21 (1H, ddd, J=0.6, 1.9, 4.9), 7.68 (1H, ddd, J=2.0, 7.2, 8.3), 7.41 (2H, dd, J=7.5, 8.3), 7.19 (1H, m), 7.15 (2H, ddd, J=1.4, 2.4, 2.9), 7.00 (1H, ddd, J=0.9, 5.0, 7.2), 6.91 (1H, td, J=0.7, 8.3); ^{13}C NMR δ_C (100 MHz); 163.7 (**Q**), 154.1 (**Q**), 147.7 (**C**H), 139.4 (**C**H), 129.7 (2**C**H), 124.6 (**C**H), 121.1 (2**C**H), 118.4 (**C**H), 111.5 (**C**H). Spectroscopic data was in agreement with that previously published.[171]

7 References

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Appendix A: Further Proof for a 3,3-Sigmatropic Shift Mechanism

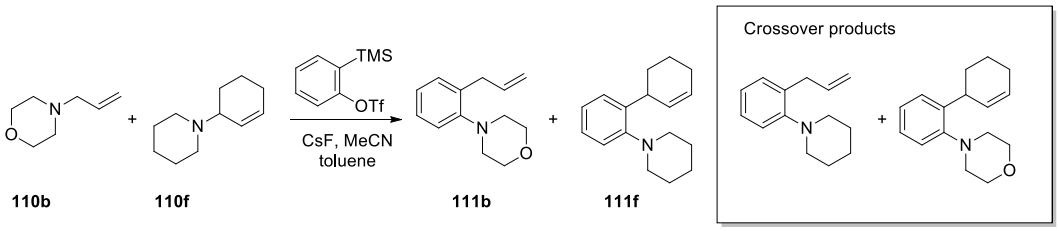
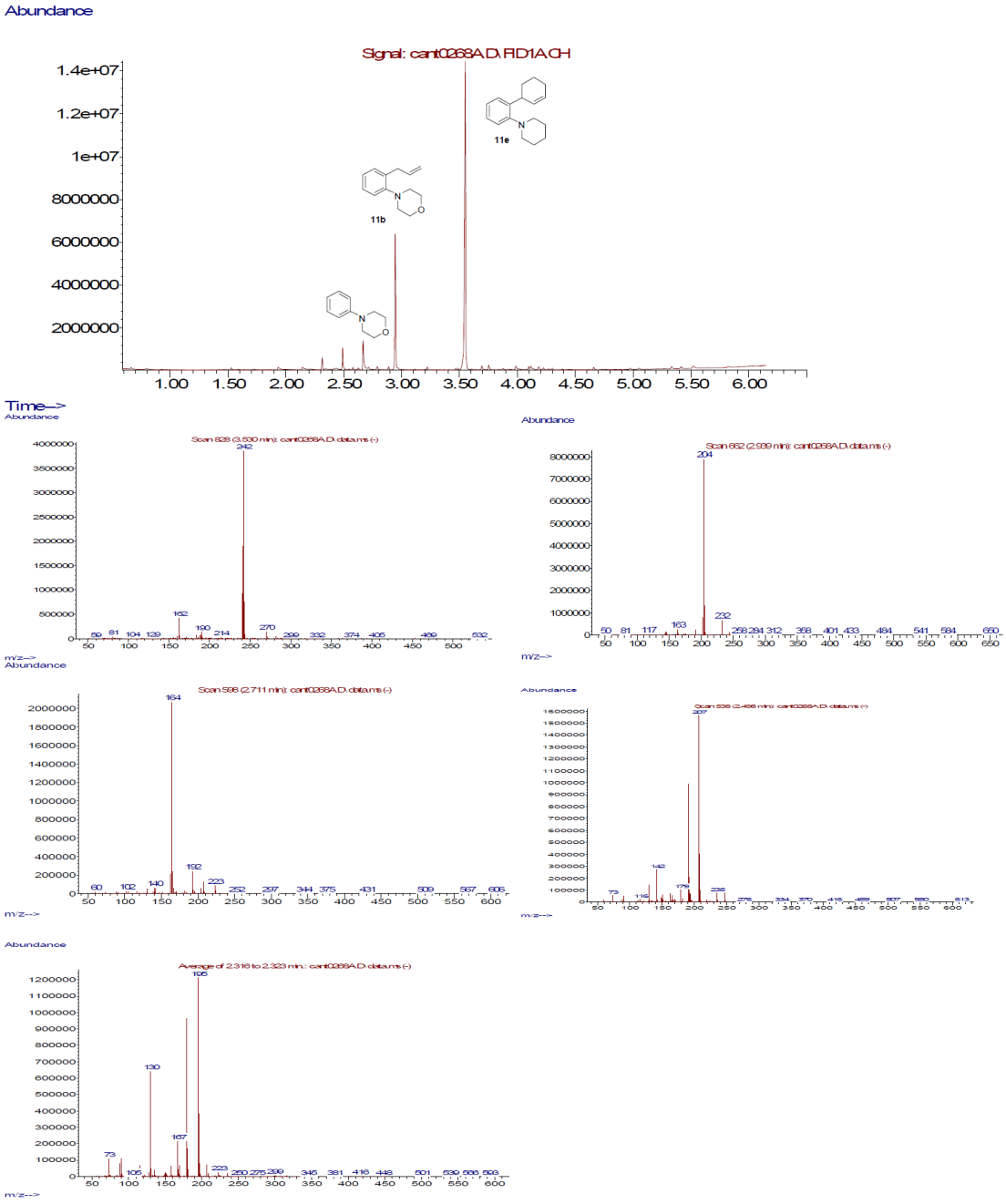


Fig A. A crossover experiment.

Presented below is the GCMS data for the crossover experiment shown above in figure A. No crossover products were detected.


Abundance
Signal: cant0268AD\FID1A,CH
1.4e+07
1.2e+07
1e+07
8000000
6000000
4000000
2000000
11e
11b
1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00
Time-->

Appendix B: A Comprehensive List of Chemicals and Conditions Tried in the Optimisation of the Generation of Benzyne from Benzoic Acid

Temperature: RT-160 °C

Only temperatures in excess of 140 °C were sufficient in the formation of triphenylene.

Starting materials: Benzoic acid, potassium benzoate, sodium benzoate, methyl benzoate, ethyl benzoate, allyl benzoate.

Benzoic acid was found to be the best substrate, the sodium and potassium salts were found to work a little and the esters not at all.

Solvents: Sulfolane, DMF, DME, DMAc, DMSO, NMP, diglyme, decalin, o-xylene, mesitylene, decane, *tert*-butanol, acetonitrile, THF.

Polar solvents such as sulfolane, DMF, DMSO and diglyme were found to work, with DMF and sulfolane giving the best results.

Catalysts: $Pd(OAc)_2$, $PdCl_2$, 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate, $Pd(MeCN)_2Cl_2$, 2'(dimethylamino)-2-biphenylyl-palladium(II)chloride dinorbornylphosphine complex, $Pd(dppf)Cl_2$ dichloro(di-μ-chloro)bis[1,3-bis(2,6-di-i-propylphenyl)imidazol-2-ylidene]dipalladium(II), chloro(di-2-norbornaylphosphino)(2-dimethylaminomethylferrocen-1-yl)palladium(II) chloro[(1,2,3-n)-3-phenyl-2-propenyl][1,3-bis(2,6-di-i-propylphenyl)4,5-dihydroimidazol-2-ylidene]dipalladium(II), $RhCl_3$, $Rh(Acac)_3$, $[Cp^*RhCl_2]_2$, Rh(Acac)cod, Grubbs catalyst 1st generation, $IrCl_3$, $[Cp^*IrCl_2]_2$, $Ir(Acac)_3$, Ir(Acac)cod, tris(norbornadiene)acetoacenato)iridium(III), chlorodihydrido[bis(2-di-i-propylphosphinoethyl)amine iridium(III), $Ni(Acac)_2$, $Ni(dppp)Cl_2$, $Cp^*Re(CO)_3$,

Many of the palladium catalysts worked in the reaction, but it was found that $Pd(OAc)_2$/ligand systems were superior. All other metals showed negative results with the exception of $Ni(Acac)_2$ which gave trace amounts of triphenylene.

Ligands: BINAP, dppm, dppe, dppp, dppb, diphenylphosphinopropane, dpph, PPh_3, 1,4-bis(dicyclohexylphosphino)butane, tricyclohexylphosphine, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, butyldi-1-adamantylphosphine, 4,6-bis(diphenylphosphino)phenoxazine, 2,2'-bipyridyl, 6,6'-dibromo-1,1'-bi-2-naphthol, 1,3,5-triaza-7-phosphaadamantane, (R)-(+)-1,1'-binaphthyl-2,2'-diamine, 1,10-phenanthroline, (2-biphenyl)di-*tert*-butylphosphine, racemic-2-di-*t*-butylphosphino-1,1'-binaphthyl, 2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl, 2-di-cyclohexylphosphino-2',6'-dimethoxy-1,1'biphenyl, 2-di-cyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'biphenyl, 2-di-cyclohexylphosphino-2',(*N*,*N*,-dimethylamino) biphenyl, $P(n\text{-}Bu)_3BF_4$.

In general only 1,10-phenanthroline and phosphine ligands worked in the reaction, in particular biphenylphosphino ligands worked well.

Oxidants: benzoquinone, oxygen, $Cu(OAc)_2$, Ag_2CO_3, $CuCl_2$, air, AgO, CuO, Ag_2O, $PhI(OAc)_2$.

$Cu(OAc)_2$ was the only oxidant that promoted this reaction.

Additives: LiOAc, CuOAc, K_2CO_3, K_2HPO_4, KOAc, AgOAc, NaOAc, Cs_2CO_3, Na_2CO_3, $N(n\text{-}Pr)_3$.

K_2HPO_4 was the only useful additive that aided this reaction.

Phase transfer catalysts: TBAC, TBAB, TBAI, Adogen 464, $EtPPh_3Br$, PBu_4Br, PPh_4Br, 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride.

All phase transfer catalysts were viable in the reaction with the exception of 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride. TBAB was found to give optimum yields.